PATHOPHYSIOLOGIC MECHANISMS AND CATHETER ABLATION IN ATRIAL FIBRILLATION

PhD Thesis

By

Cristina (Tutuianu) Vaduva, M.D.

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Cristina (Tutuianu) Vaduva, M.D.

Supervisor:

Robert Pap, M.D., Ph.D

2nd Department of Internal Medicine and Cardiology Centre

Faculty of Medicine, University of Szeged

Doctoral School of Clinical Medicine

Clinical and Experimental Cardiovascular Science

Szeged

2019

CONTENT

PUBLICATIONS RELATED TO THE SUBJECT OF THE THESIS

I. **Tutuianu C**, Szilagy J, Pap R, Sághy L. Very Long-Term Results Of Atrial Fibrillation Ablation Confirm That This Therapy Is Really Effective. J Atr Fibrillation. 2015 Aug 31; 8(2):1226. **IF 0.14**

II. Sághy L, **Tutuianu C**, Szilágyi J. Atrial tachycardias following atrial fibrillation ablation Curr Cardiol Rev. 2015; 11(2):149-56. **IF 1.35**

III. Ágoston G, Szilágyi J, Bencsik G, **Tutuianu C**, Klausz G, Sághy L, Varga A, Forster T, Pap R. Impaired adaptation to left atrial pressure increase in patients with atrial fibrillation. J Interv Card Electrophysiol. 2015 Jun 30. **IF 1.676**

IV. **Tutuianu C**, Traykov V, Bencsik G, Klausz G, Sághy L, Pap R. Association between dissociated firing in isolated pulmonary veins and the initiation and maintenance of atrial fibrillation. J Interv Card Electrophysiol. 2016 Jan; 45(1):29-35. **IF 1.826**

V. **Tutuianu C**, Pap R, Riesz T, Bencsik G, Makai A, Saghy L. Is adenosine useful for the identification of atrial fibrillation triggers? J Cardiovasc Electrophysiol. 2018 Oct 29. doi: 10.1111/jce.13779. **IF 2.873**

ABBREVIATIONS:

ABL – ablation/mapping catheter
Ado – adenosine
AF – atrial fibrillation
ATs – atrial tachycardia
AV – atrioventricular
BSA – body surface area
CFAE – complex fractionated atrial electrograms
CMC – circular mapping catheter
CS – coronary sinus
CTI – cavo-tricuspid isthmus
DCCV – direct cardioversion
DF – dominant frequency
DF – dominant frequency
DiFi – dissociated firing
EAM – electro anatomical mapping
ERP – effective refractory period
ICE – intracardiac echocardiography
IRAF – immediate recurrence of atrial fibrillation
IRAF – immediate recurrence of atrial fibrillation
Iso – isoproterenol
LA – left atrium
LAP – left atrial pressure
LAV – left atrial volum
LAVI – left atrial volum indexed
LIPV – left inferior pulmonary vein
LSPV – left superior pulmonary vein
LVEF – left ventricular ejection fraction
MA – mitral annulus
PAF – paroxysmal atrial fibrillation
PALS – peak atrial longitudinal strain
PPI – post pacing interval

PVI – pulmonary vein isolation

PVs – pulmonary veins

RIPV – right inferior pulmonary vein

RSPV – right superior pulmonary vein

SI – stiffness index

TCL – tachycardia cycle length

INTRODUCTION

Atrial fibrillation (AF) is an arrhythmia of increasing prevalence. Since the identification of trigger activity in the pulmonary vein (PVs) by Haissaguerre et al, (1) catheter ablation of atrial fibrillation (AF) has become an established therapeutic modality for the treatment of patients with AF. Over the last decades, pulmonary vein isolation (PVI) has become the mainstay of ablation treatment of atrial fibrillation. Thereby, durable PV isolation (PVI) is a highly effective therapy when PV arrhythmogenicity is responsible for PAF. However, when other pathophysiologic mechanisms are involved, the effectiveness of PVI may be limited (2). Published data in the literature suggest that success rates following ablation of AF are relatively favorable (50-70%) (3, 4, 5). The AF population is very heterogeneous, with respect to duration and type of arrhythmia, comorbidities etc, and ablation results may depend on different definitions of success, follow-up methods, type of AF and ablation strategies. The success of catheter ablation may also depend on technical aspects of the procedure and the frequency and intensity of arrhythmia monitoring.

Regardless of the ablation techniques used, ablation of AF may result in regular atrial tachycardias (ATs) or flutter, which is one of the most important proarrhythmic complications after left atrial (LA) ablation. Atrial tachycardias that occur after AF ablation can cause even more severe symptoms than those from the original arrhythmia prior to the index ablation procedure since they are often incessant and associated with rapid ventricular response, which is difficult to control using antiarrhythmic medications.

After achieving PVI, dissociated firing (DiFi) from PVs is frequently observed (6). The capability of PVs to generate an isolated ectopic rhythm may signify their arrhythmic potential and therefore predict a higher success (7). On the other hand, the presence of DiFi may be related to better quality of PVI, farther away from PV ostia, also suggesting improved outcome (8). Whether spontaneous electrical activity of isolated PVs is related to their arrhythmogenicity or only an epiphenomenon and whether observing DiFi after PVI has prognostic significance remain unclear.

Arrhythmogenic ectopy triggering AF can be identified during the electrophysiology study if spontaneously occurring or can be induced by drug challenge. Due to the spurious nature of spontaneous triggers and the laboriousness of AF provocation, empirical isolation of all PVs has become the standard in AF ablation, despite the fact that selective isolation of only the

triggering PV can achieve similar success in selected patients (9). Even if total PV isolation is pursued as a first step, identification of non-PV triggers gains importance when AF occurs despite isolated PVs (10, 11). The role of high dose isoproterenol (Iso) infusion to elicit AF triggers is well established (12, 13). Besides Iso, adenosine (Ado) or adenosine-triphosphate (ATP) is increasingly used for the induction of AF, despite the lack of systematic studies on the sensitivity and specificity of these drugs.

AIMS

For improving the outcome after AF ablation, we sought to investigate different aspects starting with a literature review (success rate, predictors and mechanism of recurrent atrial arrhythmias), pathophysiologic mechanism, assessment of the triggering PVs and identification of non-PV triggers using different drugs. First, we study the response in electrical (mechanoelectrical feedback) and reservoir function to acute pressure elevation in the normal human LA and in the LA of patients with AF. Second, we investigate whether dissociated firing in isolated PVs implies arrhythmogenicity of the particular PV and therefore, a better outcome of PVI. Third, for the identification of AF triggers we compare Ado to Iso for the induction of paroxysmal AF.

LITERATURE REVIEW

To be able to evaluate the very long-term results of atrial fibrillation ablation we conducted a systematic literature review of all relevant studies published until March 2015. A comprehensive discussion of long-term outcome of catheter ablation including parameters like type of AF, ablation strategies, the use of antiarrhythmic drugs after ablation, multiple procedures, success definitions, the frequency and intensity of arrhythmia monitoring. We have also analyzed our database of patients with paroxysmal and persistent atrial fibrillation ablation.

Definition Of Long-Term Follow-Up

In the 2012 Expert Consensus on catheter ablation of atrial fibrillation, (14) late recurrence of AF is defined as a recurrence after 12 months or more after AF ablation and the long-term success is defined as freedom from AF following the 3 months blanking period through a minimum of 36 months.

There is also consensus that all patients who undergo catheter ablation of AF should be controlled every six months for at least two years. In our review, we defined very long-term follow-up to be longer than 3 years after the index procedure.

Impact Of Type Of AF

Depending on whether patients have paroxysmal (PAF), persistent, or longstanding persistent AF, the outcome of ablation procedures differs considerably. A systematic review and meta-analysis including, mostly retrospective studies published by Ganesan et al (15) demonstrated that the single procedure success for PAF was 68.6 % at 1 year, 61.1% at 3 years and 62.3% at 5 years.

After multiple procedures (average 1.45 procedure per patient) 79% of patients were free from AF at 5 years follow-up. Comparing patients with persistent and long-standing persistent AF after a single procedure the results were less favorable, 50.8% at 1 year, and 41.6% at 3 years.

After multiple procedures, the success was definitely more promising in this population, 77.8% in the long-term, but only few studies reported the outcome of AF ablation after more

than 3 years suggesting that we need more data to definitively assess the very long-term efficacy of ablation in persistent atrial fibrillation.

An interesting question concerning the long-term recurrence and efficacy of the ablation procedure whether these interventions can prevent progression of the arrhythmia from paroxysmal to persistent form. In the study of Takigawa et al (3) during a median follow-up of approximately 48 months, AF progressed from paroxysmal to persistent in 1.2 % of patients in accordance with previous investigations where the AF progression rate was similar (1.5% -3%). (16, 17)

In contrast, the results of pharmacologic therapy are definitely worse, the reported rates vary between 5.5% and 15%/ year (18, 19). These observations suggest that the interventional therapy is better than drugs alone for preventing AF progression, which is an important aspect of long-term consequences of the arrhythmia.

Impact of Ablation Techniques

Whereas a consensus has been reached on the suitable approach for ablation of patients with paroxysmal AF, (14) no such consensus exists for patients with persistent and long lasting persistent AF regarding the optimal technology of treatment.

Numerous clinical trials demonstrated that the main mechanism of AF recurrence after PVI in the paroxysmal population is the resumption of electrical conduction between the veins and left atrial muscle. This statement is true for either the short or the long-term recurrences (see below). (15, 20) Base upon these observations we should assume that at least in PAF, the durability of venous isolation and therefore permanent electrical disconnection plays a crucial role in maintaining procedural effectiveness in the long-term.

Accordingly, any kind of procedural tool or technique which can facilitate the durable isolation of pulmonary veins can be useful. An alternative energy source that has been developed to overcome some of the disadvantages of radiofrequency ablation is cryoenergy using a balloon based technology.

A comparison (1:1 propensity score match) between cryoballoon and radiofrequency ablation showed similar long-term success rates with a recurrence rate of 45 % in both groups after a two-year follow-up (21). Neumann et al (22) reported freedom from AF in 74% of patients with paroxysmal AF and 42% with persistent AF, but the follow-up time was shorter.

Cryoablation is a new technology and it is under continuous development, but whether it can improve very long-term outcomes has to be investigated in the future. As mentioned earlier,

in patients with persistent and longstanding persistent AF the data concerning the outcomes are considerably less favorable than for PAF. The wide contrast in PVI success rates between paroxysmal and persistent AF suggested that the mechanisms can be substantially different, and probably related to electrophysiological and structural remodeling of left atrial substrate.

Not surprisingly, current approaches designed to target persistent AF are mainly based on modification of the atrial substrate, but exhibit remarkable differences, and a widely accepted uniform strategy is missing. Different ablation strategies, including the ablation of complex fractionated atrial electrograms (CFAEs), (23) linear lesions in the LA, (24) ablation at the maximal high dominant frequency spots, (25) rotor ablation (26) have been developed as an add-on to PVI to improve the outcome in this group.

They reported the success rate of other techniques: linear ablation in addition to PVI (11-74%), posterior wall isolation (42-50%) CFAE ablation (36-68%) or „stepwise" ablation approach (38-62%). The integration of repeat procedures and addition of previously ineffective antiarrhythmic drugs further improved clinical success. Our approach is wide area antral circumferential ablation for paroxysmal and persistent patients as well, with complete isolation of PVs, without creating additional lesions in the LA. During the procedures we use open irrigation radiofrequency catheters and a combination of EAM and intracardiac echocardiography to enhance the anatomical orientation and the monitoring of catheter-tissue contact. After a mean of 18 months follow-up time the recurrence rate after single procedure was 52% and 61%, after multiple procedures was 19% and 29%, in a paroxysmal and persistent cohort respectively (Fig. 1.)

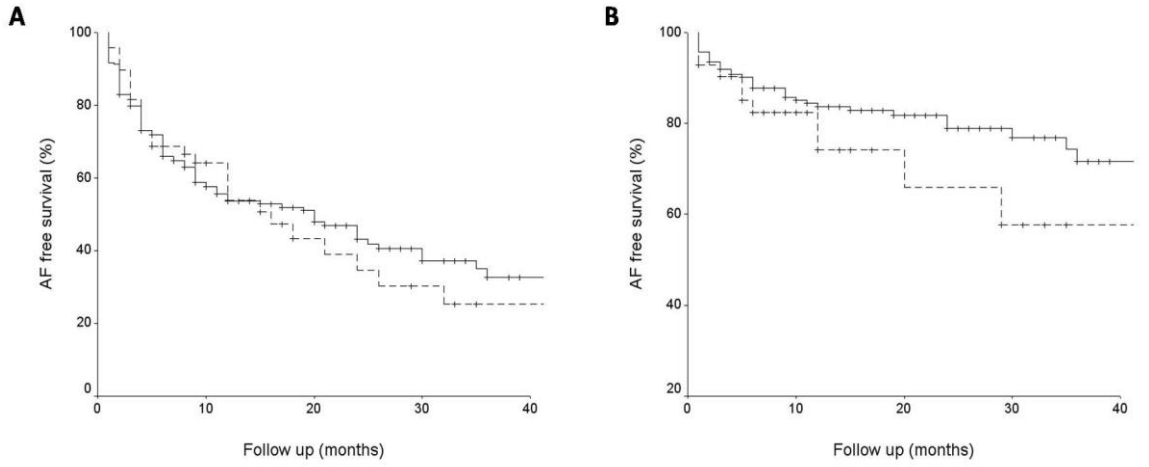

Figure 1. Kaplan-Meier curve representing the arrhythmia free survival after single ablation procedure (Panel A) and following multiple ablation procedures (Panel B) in patients with paroxysmal (solid lines) vs persistent atrial fibrillation (broken lines). Data are originating from the database of Szeged University.

Impact of Follow-up Techniques

Apart from the above-mentioned factors, the varying results reported by those studies could be attributed to substantial differences in follow-up methods. During the first year, the majority of studies performed clinical examination, electrocardiogram and 24 - hour Holter monitoring or event recorders at 3, 6, and 12 months. Beyond the first year, the intensity of follow-up is usually reduced to 1 or 2 outpatient visits per year or even based on data from referring clinicians. (27) There is a clear positive correlation between the duration and intensity of the follow-up and the arrhythmia detection rate. (28) For the short-term follow-up, 7 day Holter and trans telephonic monitoring are proven to be effective to detect asymptomatic AF episodes. Piorkowski et al. (28) showed that using serial 7-day Holter and trans-telephonic monitoring, the „real" procedural success rate decreased from 70% to 50% and 45% respectively.

The definition of long-term ablation success remains controversial because current post ablation rhythm monitoring strategies are based on symptom and/or intermittent ECG recordings and thus probably underestimate the real rate of AF recurrences. (29) Continuous monitoring like implantable loop recorders are useful tools (30) but to put these devices into an everyday practice is limited by cost, patient's compliance and high burden of false detection.

Predictors And Mechanism Of Recurrence

As we suggested earlier, the success of catheter ablation may depend on technical aspects of the procedure but also on patient related factors. Patients in whom AF recurred, exhibit specific clinical characteristics which can be considered as independent predictors of late AF recurrence. Some studies reported history of persistent AF as a predictor of very late recurrence (15, 31, 32) while other studies found that there was no significant association between the AF type and risk of recurrence. (20, 33) The heterogeneity in results across the studies can be explained by the heterogeneous definition of AF type and the differences in terminology pertaining to „long-term" follow-up.

The duration of AF history is a very important predictor of AF recurrence, (3) but other studies could not find a significant association between AF duration and AF recurrence. (34, 35)

A possible explanation is that duration of AF does not necessarily correlate with the length of the AF episodes and may not reflect the extent of atrial remodeling. (36) Other commonly identified predictors of AF recurrence are age > 65 years, left atrial diameter >24mm/m², (36) left ventricular systolic dysfunction, heart failure, structural or valvular heart disease, (15) hypertension and hyperlipidemia. (20)

These observations indicate the role of enhanced vulnerability of left atrial myocardium induced by these factors beyond the importance of trigger mechanism. Aggressive medical treatment of these conditions and risk factors reduction may improve the efficacy of AF ablation. Pathak et al. (37) reported in a recent publication that risk factor management according to American Heart Association/American College of Cardiology guidelines significantly improved the outcome of AF ablation in terms of AF burden and also generated favorable changes in cardiac remodeling.

The main mechanism of the early recurrence following atrial fibrillation ablation is the reconnection of previously isolated pulmonary veins. In contrast, in patients with very late recurrence the mechanism is not completely elucidated. Lin et al. (38) found that the majority of patients with recurrent AF undergoing a 3rd or more procedure after a mean follow-up of 36±22 months (range 12 to 119 months) had reconnected pulmonary veins with triggers originating from the culprit PVs. (Fig. 2). However, in 20% of patients, new non-PV triggers were identified at the time of 3rd or 4th procedure and the majority of non-PV triggers were mapped in the right atrium or coronary sinus.

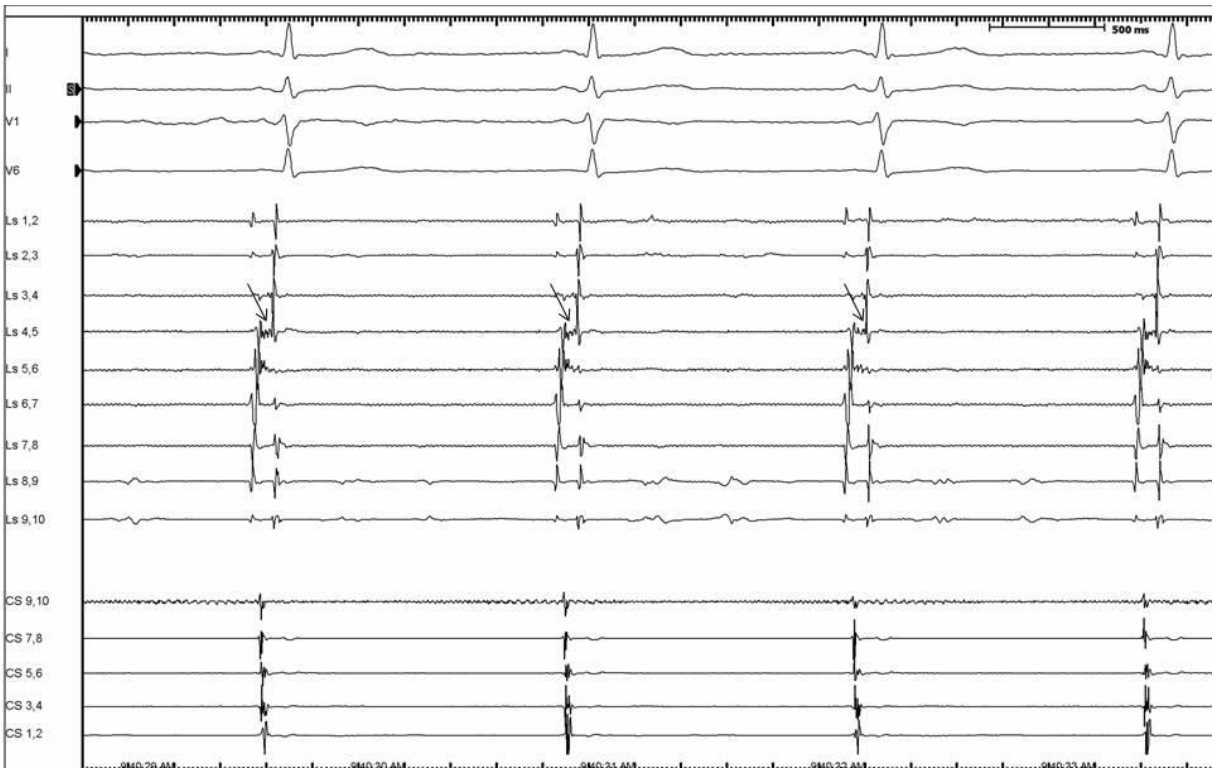

Figure 2. Late reconnection of the right inferior pulmonary veins in a 56 years old patient with PAF following 32 months the index PVI. Single ablation attempt at the level of earliest PV potentials on Lasso, 4-5 bipoles (arrow) resulted immediate isolation of the vein. All of the other pulmonary veins were isolated. Surface ECG leads I, II, V1 and V6, together with intracardiac recordings from the Lasso catheter (Lasso) placed in the right inferior pulmonary vein, and from the proximal to distal coronary sinus bipoles (CS). Tracing is originating from the database of Szeged University.

One of the most important proarrhythmic complications after LA ablation is regular atrial tachycardia or flutter. Depending on the method and extent of left atrial ablation and on the electrophysiological properties of underlying LA substrate, the reported incidence of late ATs is variable. The less is the harm caused in the LA, the lower is the incidence of late AT.

Consequently using the „initial" approach of segmental electrical PVI, which is limited to the ostia of pulmonary veins (PV) the occurrence was found to be relatively low, between 1% and 2.9% (39-42). Gaita et al. (43) concluded that in persistent atrial fibrillation, pulmonary vein isolation plus left atrial linear lesion is superior to pulmonary vein isolation alone in maintaining sinus rhythm. However, when PV ablation was achieved by placing circular lesions around the veins in the LA antrum, without targeting complete isolation of pulmonary veins, and creating additional lines in LA (e.g. mitral isthmus, and/or roof, or posterior lines) the incidence of ATs dramatically increased to even 10-fold higher, ranging from 10% to 24% (44, 45).

Sawhney et al. (46) randomized a series of patients with structurally normal hearts and paroxysmal AF to PVI with electrical isolation versus circular PV ablation plus additional lines with confirmation of completeness of circular and linear lines. After isolation of PVs without additional lines there were no cases with left ATs, but 24% had AT in the other group, despite having originally complete lines, without difference in AF recurrence rate.

The authors concluded that in patients without structural heart disease linear ablation should be avoided as an initial ablation approach. Estner and co-authors demonstrated in their randomized study (47) that comparing PVI plus linear lesions or PVI plus additional CFAE ablation-so called „spot ablation" - the overall recurrence rate was similar, but the mode of recurrence was different: regular AT was the prevailing type of arrhythmia in the spot ablation group (11 vs. 29%, p=0.03). Furthermore, Rostock et al. (48) published a stepwise approach of persistent atrial fibrillation, including PVI and extended lesions in left and right atrium.

Following this strategy, 40% of patients developed ATs during the follow-up. The prevalence of left atrial AT is 11 % in our population which is more common than in the study by Wasmer et al. (49), who published a 4% incidence in a very similar cohort recently. Organized ATs most commonly occurred several weeks to months after the AF ablation procedure, 8.8±7.7 months in our population, but sometimes during the initial attempt (either spontaneously or induced).

Mechanism - Focal AT

The mechanism of atrial tachycardia varies with the ablation technique and to establish the exact mechanism of these tachycardias can be difficult and controversial which is especially true for the focal origin.

A focal mechanism is usually suggested by the centrifugal activation pattern of the tachycardia on the electroanatomic maps.

The mechanism most commonly is microreentry, non-reentrant types are usually caused by enhanced automaticity or triggered activity. The latter tachycardias are not so common; the prevalence probably does not exceed 10% of all ATs. Following segmental pulmonary vein isolation and partially after wide area antral ablation with confirming electrical isolation these tachycardias are typically focal in nature and related to recovered PV conduction, (41, 50, 51). In our series, it was 60 % of all ATs.

Centrifugal activation pattern does not exclude reentrant mechanism by itself. This pattern can also be obtained from the exit site of a slowly conducting isthmus of a reentrant circuit, especially if the resolution of mapping is not high enough. Gerstenfeld et al. (41) performed a detailed pharmacologic and entrainment testing in a group of patients presenting with focal ATs following PVI.

These maneuvers demonstrated that most of these ATs were due to localized small reentry circuits anchored to the slow conduction areas caused by the previous ablation. Only one of six ATs showed typical focal characteristics suggesting non reentrant mechanism (52). Similarly, Deisenhofer reported a series of LA ATs, using PVI plus additional lines during the first procedure. More than one third of these tachycardias were due to small reentrant circuits related to reconnected PVs (44). Shah et al. (53), demonstrated that 73% of ATs developing after AF ablation in their study were related to narrow, critical isthmuses at the vicinity of previously ablated PV ostial sites.

Slow conduction in these areas was crucial for maintaining such a small reentrant circuit. These were 10-18 mm in size and produced rapid centrifugal activation in the rest of the LA. Interestingly, these critical isthmuses characterized by low amplitude-long duration intracardiac electrograms occupied almost half of the tachycardia cycle length and coincided with the isoelectric intervals in all 12 ECG leads, between flutter waves. (Fig. 3)

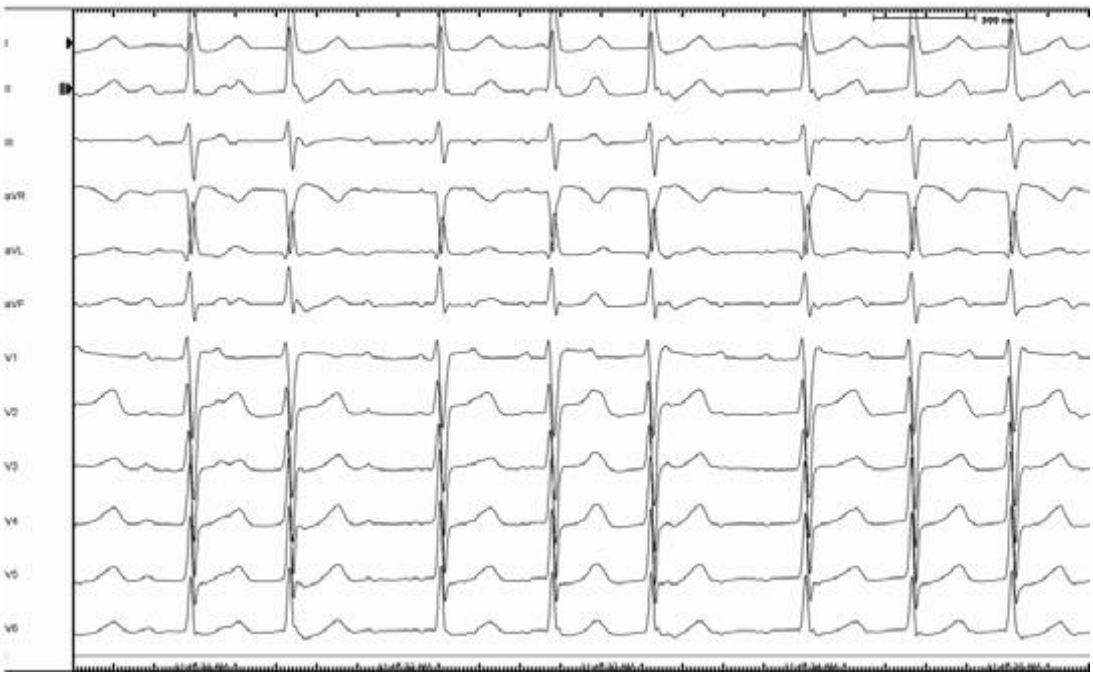

Figure 3. Twelve lead surface ECG of a narrow isthmus reentry, originating from the vicinity of right inferior pulmonary vein. Note the long isoelectric interval between discrete flutter waves.

These observations were highly consistent with the results of Yokokawa et al. (54) in terms of the observation that extremely slow conduction and adjacent anatomical barriers play a critical role in stabilizing these microreentrant circuits.

In the case of pulmonary vein tachycardia the pathologic impulse originates from the PV myocardial cells, and activates the LA through even a single recovered gap within the original lesion set. In the vast majority of cases, the rhythm within the PV is faster than in the LA, but sometimes 1:1 conduction can occur.

After closing the gap(s) between LA and PV, the tachycardia should continue as a dissociated rhythm within the PV (Fig. 4). The mechanism of these tachycardias is not clearly elucidated. Some data from the literature supported that the mechanism is non-reentrant due to enhanced automaticity and triggered activity but others demonstrated evidences suggestive of reentry inside the pulmonary veins.

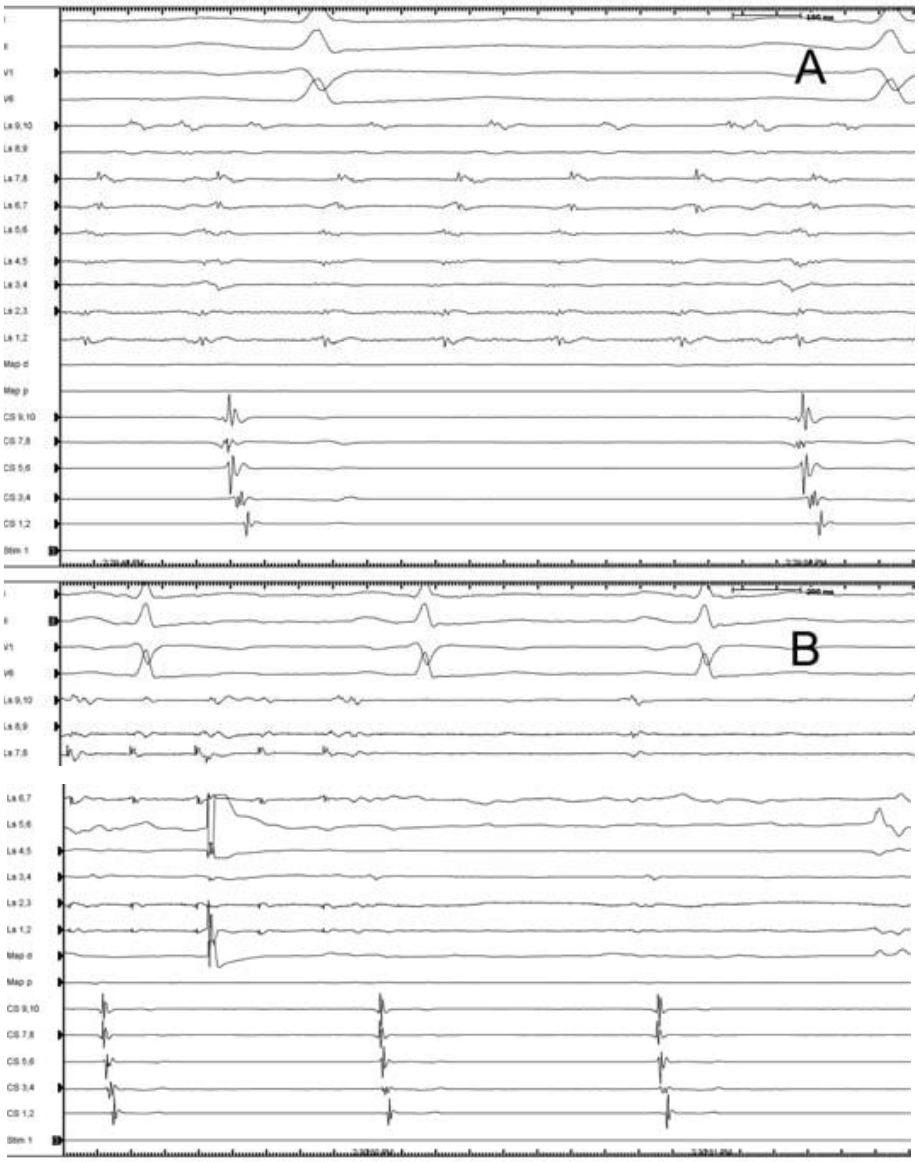

Figure 4. Rapid, regular pulmonary vein tachycardia persists within an isolated right superior pulmonary vein. The atria, outside the isolated vein are in sinus rhythm. (A). Radiofrequency ablation at the earliest spot within the vein, indicated by the ablation artifact on the 4-5 bipoles of Lasso catheter results in the termination of tachycardia. (B) Ls: lasso catheter, CS: coronary sinus catheter, Map d: mapping catheter.

Macroreentrant AT

Using anatomic ablation approaches with additional lines and/or CFAE ablation, the majority of ATs are macroreentrant, (73%-82%) which use regions of incomplete or recovered lesions and other anatomic obstacles.

These tachycardias mostly revolve around the mitral valve (perimitral flutter, 28% of cases in our experience) or less commonly around the isolated pulmonary venous ostia (roof dependent flutter, 12% of cases), rarely around septal or posterior scars or LA appendage (44, 51).

The arrhythmia circuits of these ATs are usually independent from the PVs, but sometimes the myocardial sleeves within the veins can contribute to generating such a mechanism. Satomi et al. (55) as well as Robinson et al. (56) presented clinical examples where the macroreentry circuits included the LA and PV myocardium as well, propagated via two conduction gaps located in the previous circular lesions which were relatively widely separated from each other (Fig. 5).

It should be noted that most of these tachycardias presented with focal pattern on three dimensional electroanatomic maps (3D EAM), and could have been misdiagnosed as classical focal AT without detailed entrainment mapping guided by multipolar catheter within the PVs.

Patients may also experience typical, cavo-tricuspid isthmus dependent right atrial flutter after AF ablation, which is not unusual in this population. The published prevalence of typical flutter is between 15%-30% (57, 58).

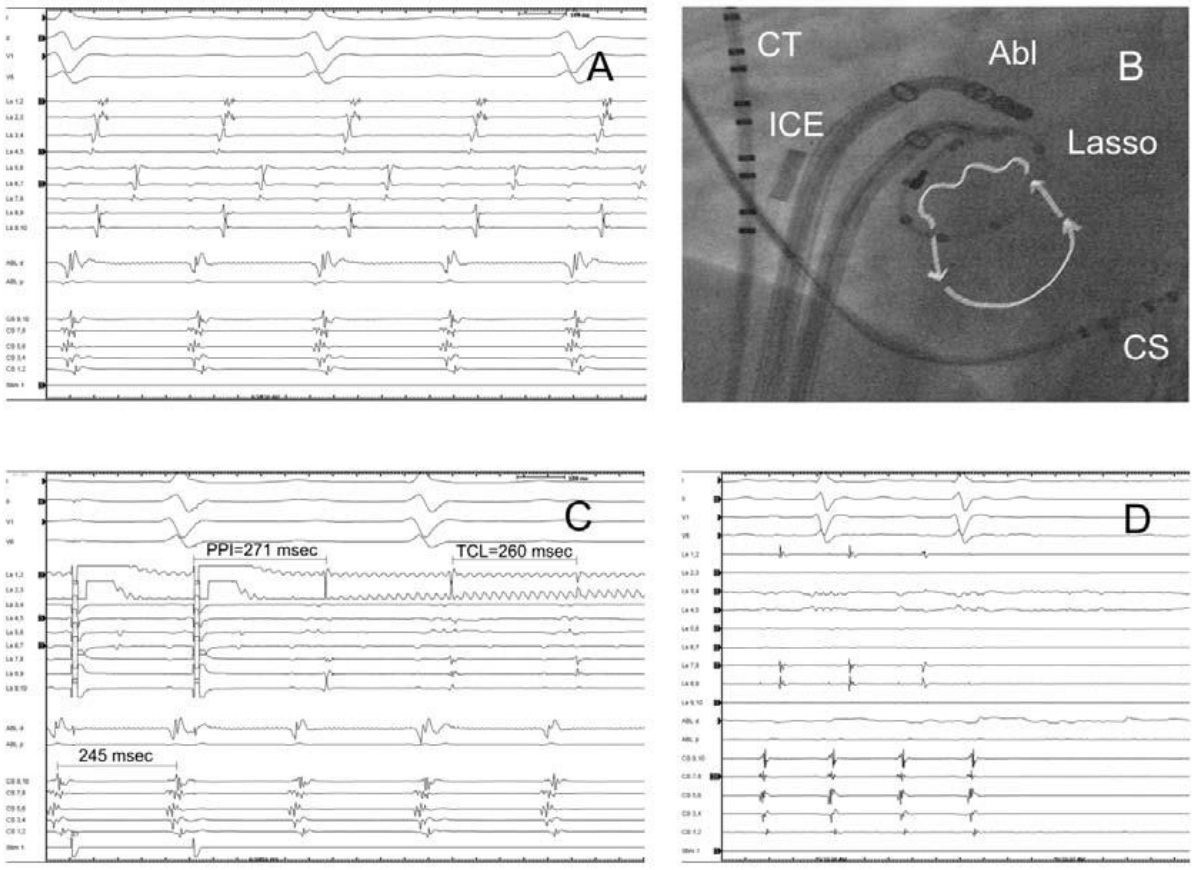

Figure 5. Gap related tachycardia originating from the circular lesion around the right inferior pulmonary vein. (A, 200mm/sec), and the corresponding catheter positions, arrows point out the direction of activation through two gaps (at lasso pole number 4-5 and 7-8) in the ablation line (B). Entrainment pacing with 245 msec from the earliest lasso bipole (4-5) showed concealed fusion and PPI-TCL was 11 msec. (C). Termination of tachycardia during ablation at the entrance (pole 4-5) (D,100 mm/sec). The vein was isolated with the second ablation at the pole 7-8 (not shown). RIPV: right inferior pulmonary vein, CT: crista terminalis catheter, ICE: intracardiac echocardiography probe, Abl: ablation catheter, Lasso: lasso catheter, CS: coronary sinus catheter, PPI: post pacing interval, TCL: tachycardia cycle length.

Clinical management

The initial treatment has to be conservative, considering that one third of ATs may resolve in time (45). The mechanism of spontaneous restoration is not clearly elucidated, but probably related to healing and changing substrate following the ablation. Understanding the mechanism (see earlier) of the AT before the redo ablation procedure could facilitate the mapping and ablation strategy of the tachyarrhythmia.

Twelve lead surface ECGs can be helpful to distinguish between macroreentrant and focal arrhythmias: continuous activation is typical for macroreentrant mechanism, whilst isoelectric baseline between P waves suggests focal arrhythmias (53).

As we already pointed out, in case of separated P waves with long isoelectric intervals in all 12 leads one can anticipate a narrow isthmus reentry, caused by little electrical activity of slowly conducting isthmuses, coinciding with isoelectric lines.

Some authors demonstrated that focal AT tends to be faster, than macroreentrant tachycardias (59), but others reported the opposite (57) or found no difference between them (49). P wave morphology can be useful to localize the source of the arrhythmia but this is very much dependent on preexisting scarring and the extent of previous ablation.

In the electrophysiology laboratory, during an ongoing AT, our approach is to use multipolar catheters in the right atrium and coronary sinus (CS) and try to entrain the tachycardia first from the cavo-tricuspid isthmus (CTI) to exclude the possibility of typical right atrial flutter.

After LA ablation of AF, sometimes typical atrial flutter shows atypical ECG findings (60) as for instance upright flutter waves in the inferior leads, which incorrectly suggests left atrial origin. However, this pacing maneuver may prevent unnecessary instrumentation of LA

After exclusion of CTI dependent flutter or other right atrial sources, entrainment pacing is suggested from the distal and proximal electrodes of coronary sinus catheter. If the post-pacing interval (PPI) minus tachycardia cycle length (TCL) is shorter than 30 msec. from those poles following termination of pacing which has resulted in atrial capture, the presence of perimitral flutter is very likely.

Once a left atrial access is obtained, atrial tachycardias can be mapped by endocardial activation mapping and/or entrainment mapping. To exclude focal tachycardias related to PV reconnection, mapping of the four pulmonary vein ostia using circular catheter is recommended. If the mechanism is small or narrow isthmus reentry - which confines usually to typical reconnection sites of PVs, (septal aspect of right, and anterior sites of left PVs) (61) - entrainment pacing will show intracardiac evidence of concealed fusion and PPI-TCL from

a limited area, demonstrating mid-diastolic or long fractionated electrograms. Using 3D EAM, small reentry is considered when the majority of the cycle length can be accounted for during mapping and the diameter of the circuit is <3 cm. Re-isolation of PV(s) usually leads to termination of tachycardias.

If the PV origin can be excluded, activation mapping has to be extended to typical sites of focal AT in LA, like posterior wall, LA appendage, and mitral annulus. The macroreentry is considered when the tachycardia is entrained with „in circuit" response from remote sites of LA, electrograms span all or most of the diastole, activation mapping accounts for at least 85% of the tachycardia cycle length, as well as the diameter of the reentry circuit is >3 cm, and continuous propagation sequence with earliest and latest activation adjacent to each other on the EAM (57, 62).

The most common form is the peri-mitral flutter traversing the mitral isthmus. In case of single loop peri-mitral circuit, there are several options to produce linear ablation lesions to terminate the tachycardia. The most common choice is the classical mitral isthmus line between the left inferior PV and the posterior mitral annulus (MA).

Usually, it is a fairly long and concave isthmus, where one can have difficulties getting good contact without using intracardiac echocardiography. Histological data confirmed that coronary sinus muscle sleeves in this location are present in up to 75% of patients, and extend onto LA isthmus musculature.

Not surprisingly, coronary sinus ablation is required in at least 70% of patients but bidirectional block cannot always be achieved (63). Another possibility is to create linear lesion from the right inferior PV to posterior MA, which is one the most difficult isthmuses because of the proximity of three different anatomical structures (right and LA and coronary sinus) and the slow pathway region.

Next option is drawing lines from the right superior PV to anterior MA. This isthmus is usually longer than the posterior mitral isthmus, and this line passes the insertion of Bachmann bundle, which is relatively thick and may prevent the creation of a transmural lesion (Fig. 6). Several studies pointed out that failure to achieve bidirectional mitral isthmus block increased the risk of developing left atrial flutter. Anouseh et al. demonstrated (64) that in patients in whom mitral isthmus block was not achieved, there was a fourfold risk of occurrence of subsequent ATs.

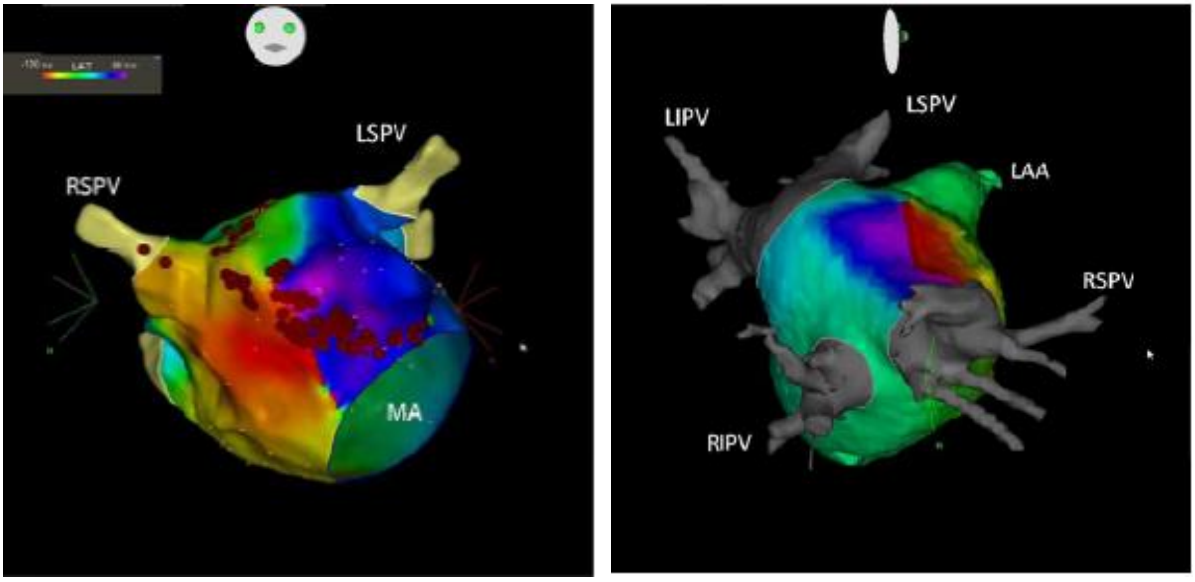

Figure 6. **A** Perimitral reentry propagating around the mitral valve in counterclokwise direction on three dimensional CARTO activation map. Red dots represent the ablation line which was created between the anterior mitral annulus and the right superior pulmonary vein. Pannel B Roof dependent flutter propagating around the right sided pulmonary veins on three dimensional CARTO activation map with CT integration in right lateral view. RSPV: right superior pulmonary vein, RIPV: right inferior pulmonary vein, LSPV: left superior pulmonary vein, LIPV: left inferior pulmonary vein, LAA: left atrial appendage, MA mitral anulus.

Macroreentry tachycardias around the isolated right of left side veins are less common, and in most patients completion of LA roof line leads to termination of tachycardias.

METHODS

Study group 1

Consecutive patients with manifest or concealed left-sided accessory pathway, without a history of AF (controls) and patients with paroxysmal AF scheduled for PVI, who had no symptomatic and/or documented AF episodes in the week prior to the procedure, were included. Exclusion criteria were persistent AF, CHADS2 (Congestive Heart Failure, Hypertension, Age, Diabetes, Stroke [Doubled]) score >2, previous LA ablation or open heart surgery, heart failure, reduced left ventricular function, and moderate to severe mitral regurgitation.

Electrophysiologic procedures

Informed consent was obtained and antiarrhythmic drugs have been discontinued for at least five half-lives at the time of the procedure. Using right ± left femoral vein access single (control patients) or double (AF patients) transseptal puncture was performed using 8.0 or 8.5 French transseptal sheaths (Fast-Cath, St. Jude Medical, St. Paul, MN, USA), under intracardiac echocardiographic guidance.

The side arm of the transseptal sheath was connected to a disposable pressure transducer (Combitrans, B. Braun, Melsungen, Germany), which was positioned and zeroed at a reference level 5 cm below the left sternal border, at the fourth intercostal space (65). Pressure was recorded at a sampling rate of 977/s by the CardioLab EP Recording System (GE Healthcare, Chalfont St Giles, UK).

Pacing protocol

The protocol was performed after the completion of the catheter ablation procedure, during the waiting period. At each site, pacing was performed with 2-ms stimulus duration, at twice diastolic threshold. Simultaneous atrioventricular (AV) pacing was carried out to produce an acute increase in LA pressure.

LA ERP was determined both during simultaneous AV pacing and during atrial pacing at the same cycle length to control for the effect of the preceding cycle length on atrial ERP (Fig. 7). In AF patients, the atrial pacing catheter was positioned in the LA appendage; while in control

patients, LA ERP was determined by pacing from the distal bipole of the coronary sinus (CS) catheter to avoid the need for a second transseptal puncture.

This has been previously shown to reflect LA ERP well (66, 67). Simultaneous AV pacing at a cycle length of 500 ms was carried out for at least 3 min to allow stabilization of pressure. Then, after every 30th drive stimulus progressively more premature (5-ms steps) atrial stimuli were introduced, without a pause in the drive train.

LA ERP was defined as the longest coupling interval of the extrastimulus that failed to capture the atrium twice in succession.

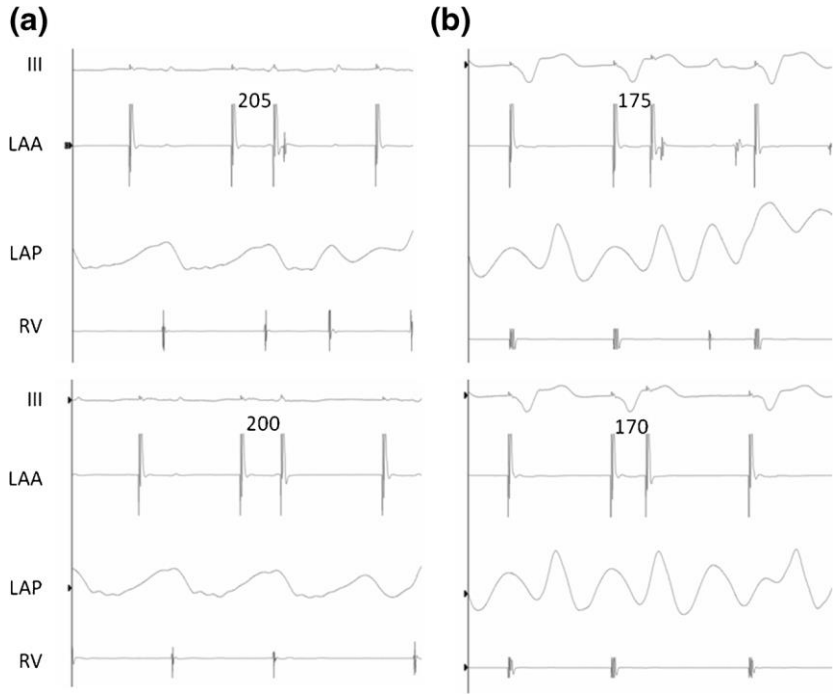

Figure 7. Determination of LA effective refractory period (ERP) during atrial pacing (a) and during simultaneous AV pacing (b). LAA LA appendage, LAP left atrial pressure, RV right ventricle.Coupling intervals (CI) of extrastimuli are shown in milliseconds. ERP is defined as the longest CI without atrial capture

Echocardiographic measurements

All patients underwent comprehensive two-dimensional transthoracic echocardiography examination using a commercially available ultrasound machine (Vivid I, GE Medical Systems, Horten, Norway) equipped with a 2.5–3.5-MHz phased array transducer and software application for two-dimensional speckle tracking-based strain imaging.

LA volumes were calculated using the biplane method of disks (modified Simpson's rule), in the apical 4- and 2- chamber view at end-systole (maximum LA size), and a mean value of volume was obtained (68).

LA volumes were indexed (LAVI) to body surface area (BSA). Mitral annular velocity was evaluated by tissue Doppler in the pulsed-wave mode (69).

Assessment of left atrial reservoir function

Particular attention was paid to obtain an adequate twodimensional- grayscale image, allowing obvious delineation of LA wall and extracardiac structures.

The frame rate was set between 60 and 80 frames per second. Three consecutive heart cycles were recorded at baseline and immediately after simultaneous AV pacing (Fig. 8). Recordings were processed using acoustic-tracking software (EchoPac PC version 110.1.8, GE Healthcare, Horten, Norway), allowing off-line semiautomated analysis of speckle tracking-based strain (70).

In the end-diastolic/systolic frame, the atrial endocardial border was marked by a point-and-click method. After automatic creation of a region of interest, the LA wall was divided into six regions, and segmental tracking quality was analyzed (Fig. 8).

The reference point was set at the onset of the QRS, and the average positive peak atrial longitudinal strain (PALS), which corresponds to LA reservoir function, was measured (Fig. 8). Values from the three consecutive cycles were averaged (71).

The LA stiffness index (SI) was calculated as mean LA pressure (LAP)/PALS(72)

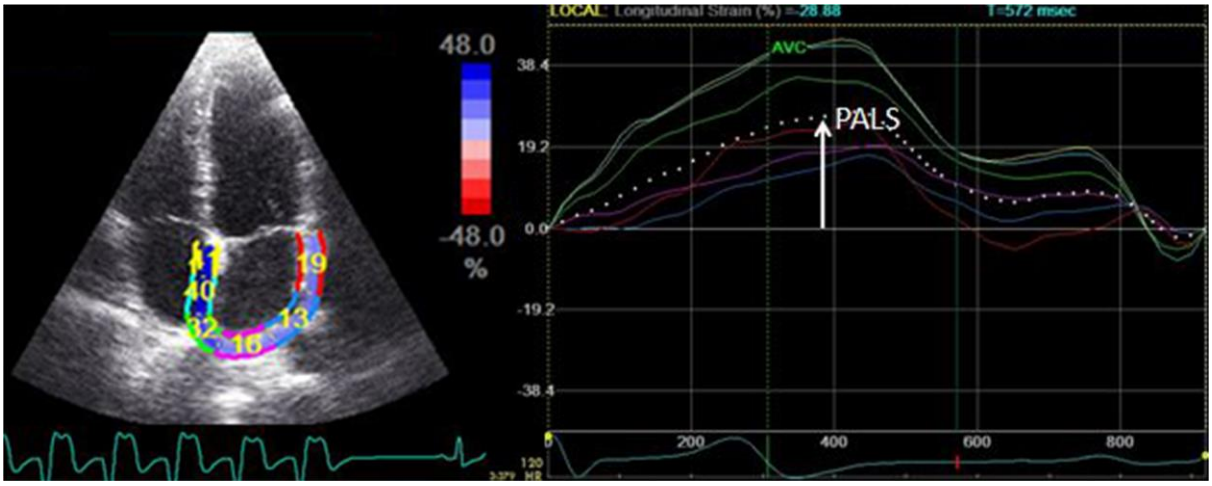

Figure 8. Measurement of peak atrial longitudinal strain (PALS) immediately after simultaneousAV pacing. The dashed curve represents the average PALS.

Study Group 2

Thirty-one consecutive patients undergoing their first PVI for drug-refractory, symptomatic PAF (53±9 years old, 17 men) were prospectively studied.

All patients gave their written informed consent to participate in the study. Exclusion criteria were previous left atrial (LA) catheter ablation or open-heart surgery, persistent AF, severe valvular heart disease, or LA thrombus.

Patients without inducible sustained PAF during the study (two patients) and those with PAF triggers originating from extra-PV sites (two patients) were also excluded.

Electrophysiologic procedure

Patients were on oral anticoagulation for at least 3 weeks before the ablation, and transesophageal echocardiography was performed to exclude any atrial thrombi before the procedure.

All antiarrhythmic drugs were discontinued for at least five half-lives except amiodarone which was discontinued 1 month prior to the procedure. The study was performed as described previously (73). Briefly, under conscious sedation (midazolam ±fentanyl), following femoral venous access, two decapolar steerable catheters (interelectrode spacing 2–5–2 mm, Dynamic Deca; Bard Electrophysiology, Lowell, MA, USA) were positioned in the coronary sinus and the posterolateral right atrium.

The LA and the PVs were mapped through double transseptal puncture. Intracardiac echocardiography (ICE) (AcuNav; Acuson Corp., Mountain View, CA, USA) was used for performing the transseptal puncture and to guide catheter positioning. A decapolar circular mapping catheter (CMC) (Inquiry Optima, St Jude Medical, Irvine, CA, USA) was positioned at the left PV antrum overlying both left PVs, and a 3.5 mm irrigated-tip mapping catheter (Navistar Thermocool, Biosense Webster, Diamond Bar, LA, USA) was positioned on the right PV carina. (Fig 9)

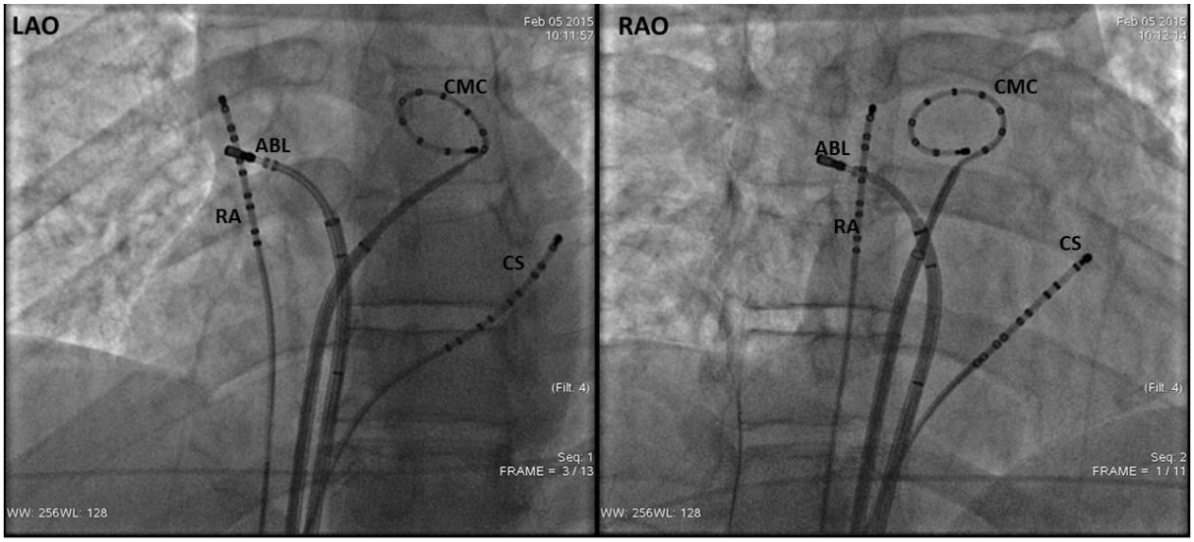

Figure 9. Left anterior oblique (LAO) and right anterior oblique (RAO) view showing the two decapolar catheters placed in the coronary sinus (CS) and right atrium (RA), circular mapping catheter (CMC) in the left pulmonary veins (PVs) and mapping catheter (ABL) in right PVs.

Assessment of the triggering PVs and signal analysis

The CMC was positioned at the left PVantrum overlying both left PVs, and the mapping catheter was positioned on the right PV carina. If the patient presented in sinus rhythm, PAF was induced by isoproterenol infusion, starting at 3 μg/min with incremental doses of 5μg/min until PAF was induced, the maximum dose of 20 μg/min was reached, or the patient developed side effects.

If the patient was in AF, first, we performed transthoracic electrical cardioversion before PAF induction. Ectopic activity triggering a PAF episode was identified, and the origin was determined based on the endocardial activation sequence and by comparison to paced activation sequences from PVs as well as observing LA-PV electrogram reversal as previously described (73). Triggering activity was considered to originate from the right PVs when earliest activation and LA-PV electrogram reversal were recorded using the mapping catheter at the right PV carina.

When earliest activation was recorded using the CMC, left upper or lower PV origin was determined based on the radiographic position of poles recording the earliest activity. After induction, isoproterenol administration was stopped and further recordings were made after a 5-min washout period.

During sustained PAF, the CMC was used to record sequentially from each PV ostium. Signals were recorded for at least 30 s at a sampling rate of 997 Hz using a digital EP recording system (GE CardioLab; General Electric, Milwaukee, WI, USA) and were stored for offline analysis.

Intracardiac recordings were analyzed, utilizing a custom-designed computer application prepared with the LabView software package (National Instruments, Austin, TX, USA). Signals were filtered between 30 and 500 Hz, rectified, and low-pass filtered at 20 Hz. A fast Fourier transformation (FFT) was performed on two consecutive 5-s episodes from each bipole of the CMC. The frequency spectrum in the 3–15 Hz range was obtained, and the peak with the highest power was determined as the dominant frequency (DF).

Noisy and highly disorganized signals (organization index<0.25) were excluded from the analysis (73). The DFs of consecutive 5-s episodes were averaged, and the maximum DF value of all bipoles was taken as the DF of that PV and used for analysis (Fig. 10).

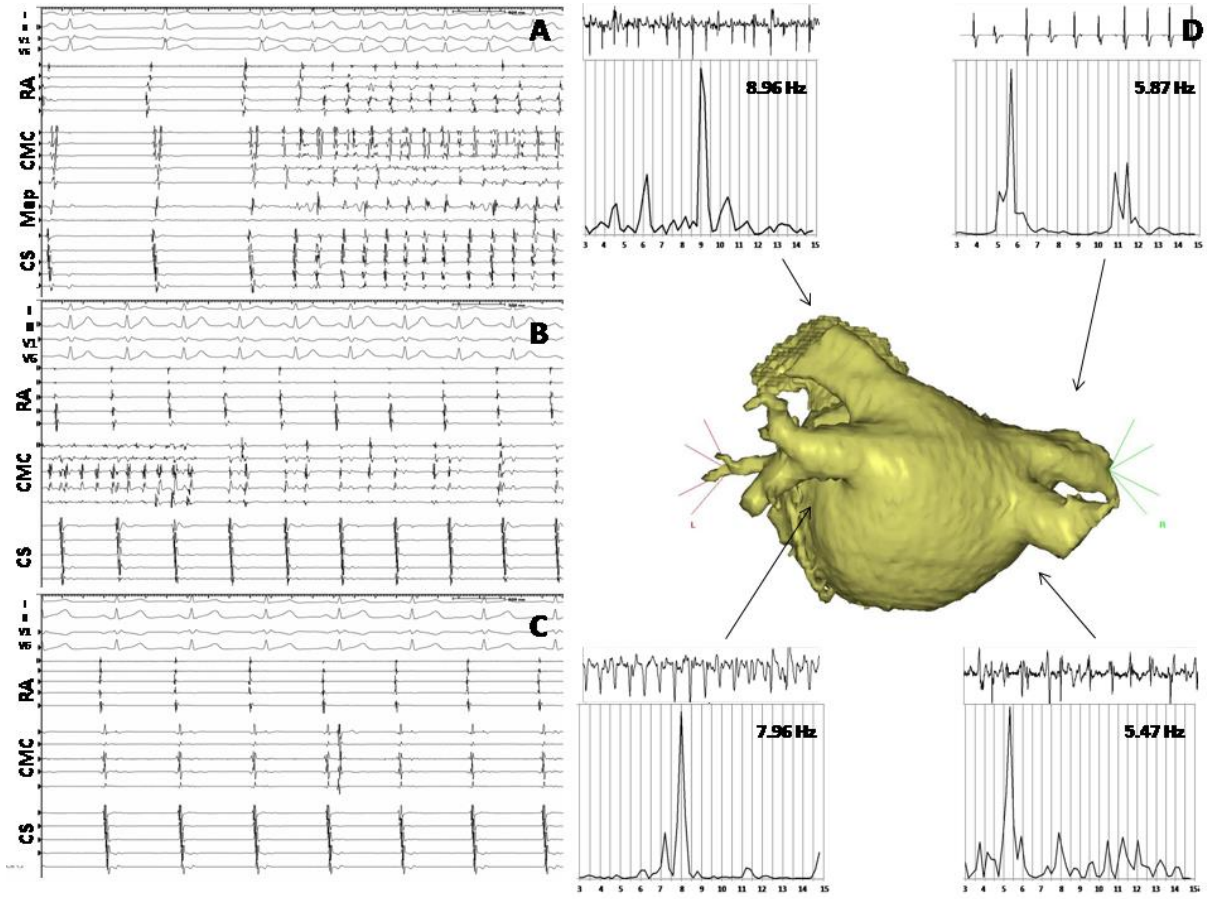

Figure 10. Surface ECG leads I, II, V1, and V6, together with intracardiac recordings from the right atrium (RA) and circular mapping catheter (CMC) placed in the left pulmonary vein antrum (a), left superior pulmonary vein (LSPV, b), and left inferior pulmonary vein (LIPV, c) and from the proximal to distal coronary sinus (CS). Atrial fibrillation is initiated by rapid discharge from the LSPV (a). Following isolation of the vein, sustained dissociated rhythm with intermittent burst activity was recorded (b). Sporadic dissociated activity was recorded in the LIPV after isolation (c). In the right pulmonary veins, there was no dissociated activity after isolation. Dominant frequency (DF) distribution during sustained atrial fibrillation in the same patient (d)

Assessment of DiFi

After electrical disconnection of all PVs, each PV was assessed periodically during a 30-min waiting period for the presence of DiFi.

The CMC was positioned in one PV for 30 s and then moved to the next, repeating periodically during the waiting period.

Rhythm in the PV was classified as follows: 1=absent (if there was no electrical activity at all), 2=sporadic DiFi (scarce and fortuitous occurrence of dissociated potentials without a regular rhythm), and 3=sustained DiFi (regular ectopic rhythm or isolated PV tachycardia) (Fig. 10 b,c).

Measurement of the PV ostial area

The LA and PVs were segmented from high-resolution computed tomography (CT) volumes using the CARTO system (Biosense Webster, Baldwin Park, CA, USA), and cut planes were positioned to separate the PVs from the body of the LA.

Using area measurement tools of the CARTO system, we measured the cross-sectional area and the perimeter of the ostium of the PVs. We chose to determine the area of the ostium of PVs because it can be measured with greater precision than the mean diameter (74-75).

Follow-up and redo procedures

All patients had a follow-up visit at 3, 6, and 12 months. Seven-day Holter monitoring was performed when a patient had no symptoms at least 6 months after ablation to reveal asymptomatic recurrence or when patients reported symptoms suggestive of recurrence without documented arrhythmia.

In case of recurrence, patients were offered a second procedure, during which reisolation of reconnected PVs was performed. No additional ablation of non-PV triggers or substrate outside the PV antra was undertaken.

Since permanent isolation of PVs often requires a second attempt, we evaluated the success of PVI after the last procedure and defined it as freedom from any sustained (>30 s) atrial arrhythmia (symptomatic or asymptomatic), off antiarrhythmic drugs.

Study Group 3

Forty patients (16 women, mean age 60±12 years) with paroxysmal AF, referred for catheter ablation comprised Study Group 3. The study was approved by the Institutional Review Board of the University of Szeged (no. 41-83).

All patients gave their written informed consent to participate in the study. Exclusion criteria were previous left atrial (LA) catheter ablation or open heart surgery, persistent AF, severe valvular heart disease or LA thrombus. Patients were prospectively included and received Ado and Iso for induction in a randomized order (76).

Drug Challenge

If the patient presented in AF, DCCV was performed to restore sinus rhythm and evaluate for spontaneous re-initiation and identifying post cardioversion AF triggers. If the presenting rhythm was sinus or AF was not spontaneously reinitiated after the cardioversion, we proceeded with the drug challenge.

Isoproterenol (Iso) was infused via a short femoral venous sheath in incremental doses starting at 3μg/min and increasing after 3-5 minutes to 5 μg/min, 10 μg/min, 15 μg/min, and a maximum dose of 20 μg/min, until induction of AF or intolerable side effects occurred.

Adenosine (Ado) was administered into the right atrium (RA) via one long transseptal sheath that was pulled back in the RA. A quick bolus of 18 mg was given flushed with 5-10 ml of saline. A second dose of 36 mg was administered if AF was not induced after the first dose. Ectopic activity triggering an AF episode was identified and the origin determined based on the endocardial activation sequence, as described above for Study Group 2. Triggers of AF were considered to arise from the left PVs if the earliest activation and LA-PV electrogram reversal was recorded on the CMC and from the right PVs if the earliest atrial activation was recorded on the mapping catheter positioned at the right PV carina. If earliest atrial activation during bursts of ectopic activity initiating AF was recorded at any of the CS or RA bipoles, then these structures were identified as the origin of triggers. (Fig 11)

The order in which the two drugs were administered (Iso first or Ado first) was randomized in a 1:1 fashion. When sustained AF was induced and did not terminate after a few minutes, DCCV was performed and the second drug was administered after a 5-minute waiting period. In cases when immediate recurrence of AF (IRAF) occurred after DCCV, drug challenge was terminated and we proceeded with ablation. We determined the effectiveness of the two drugs

in inducing AF and compared them with each other and spontaneous AF episodes in terms of the location of AF triggers.

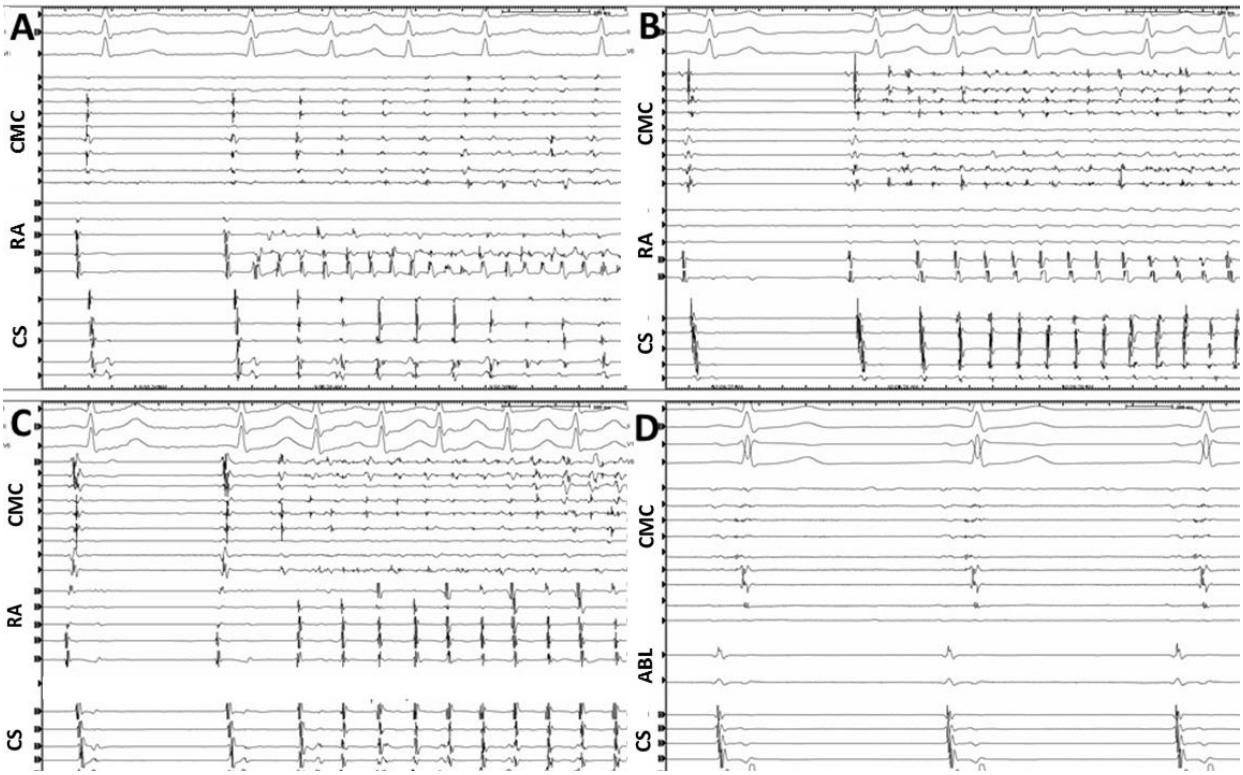

Figure 11. Surface electrocardiogram lead I, II, V6 along with intracardiac recordings from right atrium (RA), coronary sinus (CS) and circular mapping catheter (CMC) placed in the pulmonary vein (PV) antrum, during initiation of atrial fibrillation. Panel (A) during adenosine infusion AF was induced from RA. Spontaneously (Panel B) and during isoproterenol infusion (Panel C) AF was induced from the PVs. Paper speed=75mm/s. During redo procedure only the previous triggering pulmonary vein was reconnected (Panel D). Paper speed=100mm/s.

Catheter ablation

In patients undergoing a PV isolation procedure a 3-dimensional electroanatomic shell of the LA was created. Circumferential, irrigated radiofrequency ablation lesions were delivered around ipsilateral PVs using the mapping catheter, with the endpoint of electrical isolation manifested in exit and entrance block between LA and PVs.

The decision to selectively isolate only the left or right PVs - whichever were shown to be arrhythmogenic during drug challenge - or empirically isolate all 4 PVs was at the discretion of the operator.

However, in case of a redo procedure all 4 PVs were isolated, irrespective of the initial approach.

Statistical analysis

Continuous variables are reported as mean±SD and compared using one-way analysis of variance (ANOVA) and Student's t test.

Categorical variables are presented as percentage and compared using the chi-square test. Kaplan-Meier survival analysis was used to estimate the mean time to recurrent AF after the procedure. Survival curves were compared using the log-rank test.

All statistical analyses were performed using the SPSS software version 16 (IBM Inc., NY, USA). A p value <0.05 was considered statistically significant.

RESULTS

Acute pressure elevation in controls and patients with AF

In Study Group 1 eleven controls and 16 patients with paroxysmal AF were included. Controls were younger and had smaller LA volume index (LAVI), without further differences in clinical characteristics (Table 1). Patients with AF had higher mean (mLAP) and peak (pLAP) invasive LA pressures at baseline (8.3±4.7 vs. 5.1± 3.1 mmHg, p=0.048 and 20.8±8.8 vs. 14.6±5.7 mmHg, p= 0.015, respectively), compared to controls. Baseline LA PALS was significantly lower (15.1±5.1 vs. 21.6±6.2 %, p=0.006), while baseline SI was higher (0.69±0.75 vs. 0.28±0.22, p=0.015), pointing to diminished LA reservoir function in patients with AF. At the same time, LA ERP was longer at baseline in AF patients, compared to controls (242.3±33.4 vs. 211.7±15.6 ms, p=0.017).

	Controls	AF patients	p-value
Age (year)	42.2±21.1	60.3±8.8	0.019
Female (%)	22	31	0.629
BSA (m^2)	1.91±0.22	1.98±0.22	0.381
Hypertension (%)	27	56	0.137
Diabetes (%)	0	0	
$CHADS_2$ score	0.22±0.44	0.75±0.68	0.084
LVEF (%)	64.7±6.8	59.8±3.7	0.189
E_a (cm/s)	12.0±2.6	10.4±3.3	0.331
LAVI (ml/m^2)	32.4±11.4	59.4±12.1	<0.001

Table 1. Baseline clinical and echocardiographic parameters

Left atrial pressure elevation

During simultaneous AV pacing, mLAP rose by the same extent in controls and AF patients (mean change 12.6±7.4 vs. 12.6±7.5 mmHg, p=0.980). At the same time, LA PALS decreased (from 15.1±5.1 to 11.6±3.3 %, p=0.008) and SI increased (from 0.69±0.75 to 1.29±1.17, p<0.001) in patients with AF, while they remained unchanged in controls (from 21.6±6.2 to 22.9±7.1 %, p=0.405 and from 0.28±0.22 to 0.45±0.43, p=0.10, respectively). With pressure elevation, LA ERP decreased in AF patients (from 242.3±33.4 to 215.9 ±26.3 ms, p=0.003) but was not changed significantly in controls (from 211.9±16.7 to 206.3±19.6 ms, p=0.276) (Fig. 12).

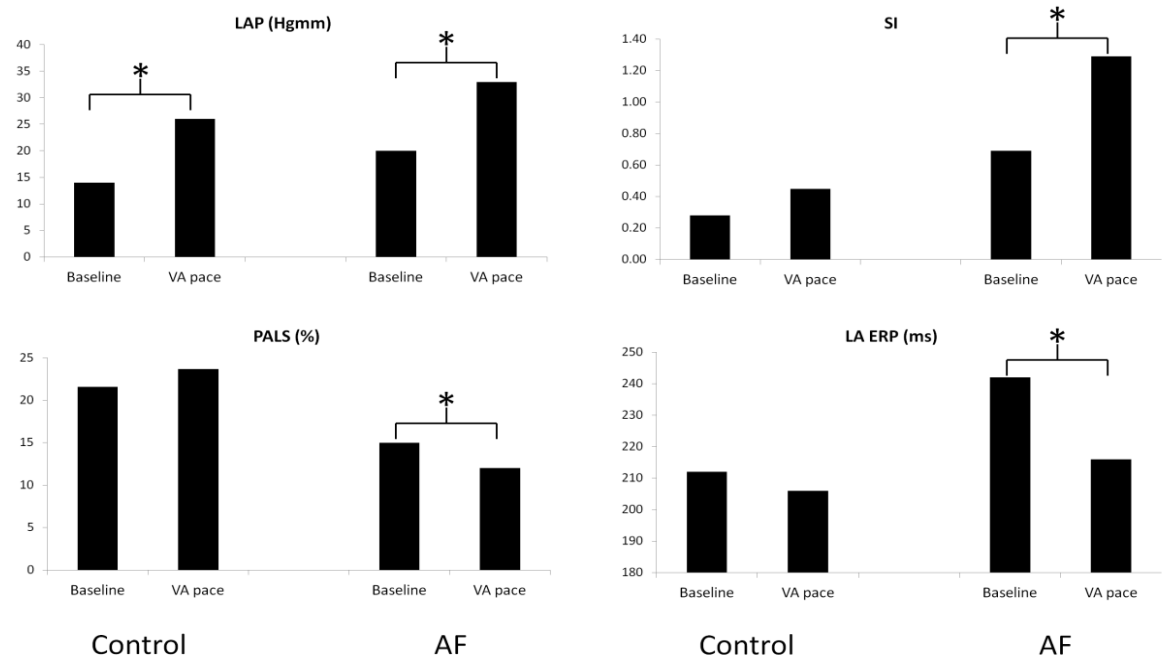

Figure 12. Changes in mean LA pressure (LAP), LA strain (PALS), stiffness index (SI), and refractory period (ERP) in response to simultaneous AV pacing in controls and AF patients. Stars mark significant ($p<0.05$) changes.

Follow-up

Four of 16 AF patients (25 %) experienced arrhythmia recurrence after pulmonary vein isolation, during 16±7 months of follow-up. Patients with recurrence had lower baseline LA reservoir function (PALS = 10.7±3.2 vs. 16.7±4.0 %, p=0.036), compared to those without.

Association between dissociated firing in isolated pulmonary veins and atrial fibrillation

Baseline characteristics of the patients from Study Group 2 are presented in Table 2. PAF triggers were found to originate from the left superior PV (LSVP) in 20 (65%) patients, from the left inferior PV (LIPV) in 5 (16%) patients, and from the right PVs in 6 (19%) patients. Electrical isolation of PVs by circumferential ablation was achieved in all patients. Fourteen (45%) patients had DiFi after PVI in at least one and 7 of them in more than one PV. It was recorded most commonly from the left upper (84%) and lower (67%) and less commonly from the right upper (31%) PVs. Out of the 23 PVs with DiFi, 13 (57%) showed sporadic ectopic beats while 10 (44%) had sustained ectopic rhythm or isolated tachycardia. No further ablation was performed to abolish this dissociated rhythm. There was no difference in size between PVs with or without DiFi (5.9±1.2 vs. 5.6±1.0 cm ostial perimeter, p=0.40, and 2.7±1.1 vs. 2.4±0.9 cm^2 ostial area, p=0.55).

Variable	No DiFi	DiFi	p value
Age (years)	54 ± 9.6	52 ± 8.5	0.27
Men (%)	41	71	0.19
PAF duration (months)	63.5 ± 53.3	58.9 ± 67.4	0.42
Hypertension (%)	65	69	0.79
Coronary disease (%)	6	8	0.84
Diabetes (%)	12	8	0.71
Left atrial diameter (mm)	45.08 ± 3.4	45.45 ± 6.9	0.43
LVEF (%)	61 ± 6.28	64.81 ± 6.54	0.08

Table 2. Clinical characteristics of patients with and without dissociated firing (DiFi) after PVI for paroxysmal atrial fibrillation (PAF).

Association between PV triggers and DiFi

Triggering PVs more commonly showed any DiFi, compared to nontriggering PVs (68 vs. 27 %, p=0.003) and more commonly had sustained DiFi (53 vs. 0 %, p<0.001) (Fig. 13). Thus, the triggering vein was more likely to have dissociated ectopy after isolation.

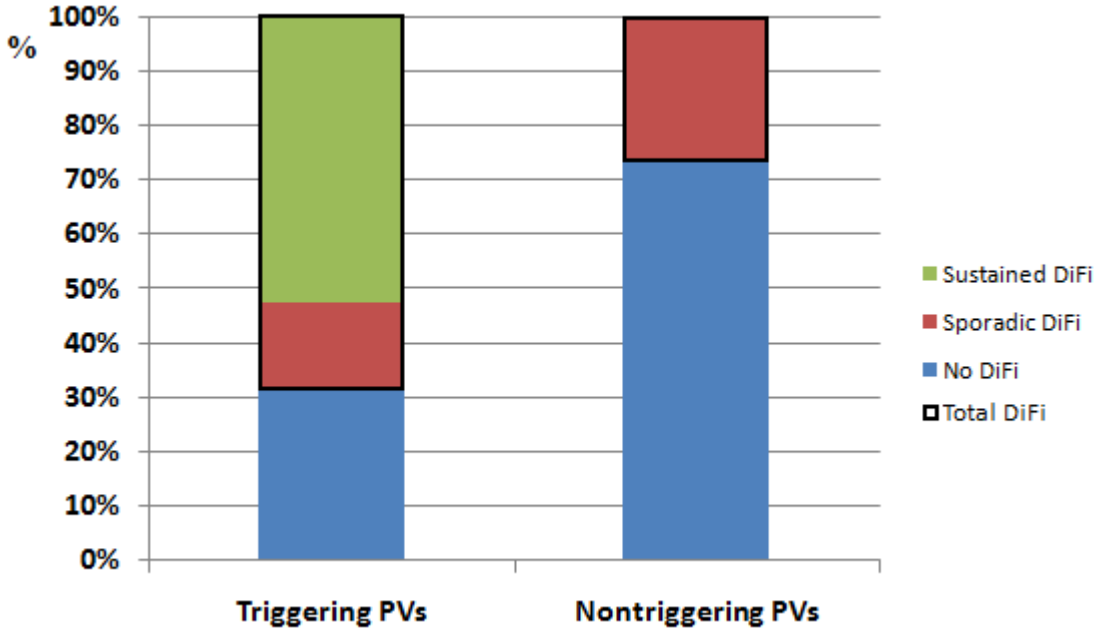

Figure 13. Distribution of the different types of dissociated firing (DiFi) following isolation in PVs with atrial fibrillation triggers versus nontriggering PVs.

Association between DF and DiFi

During sustained PAF, PVs with any DiFi showed faster maximal DF compared to PVs without DiFi (7.1±1.3 vs. 5.9± 1.1 Hz, p=0.001). Higher maximal DF was recorded in PVs with sustained versus sporadic DiFi versus PVs without DiFi (7.5±0.9 vs. 6.8±1.6 vs. 5.9±1.1

Hz, respectively, p=0.002) (Fig. 14). The maximal DF was higher in triggering PVs, compared to nontriggering ones (8.02±1.64 vs. 6.53±1.36, p<0.001).

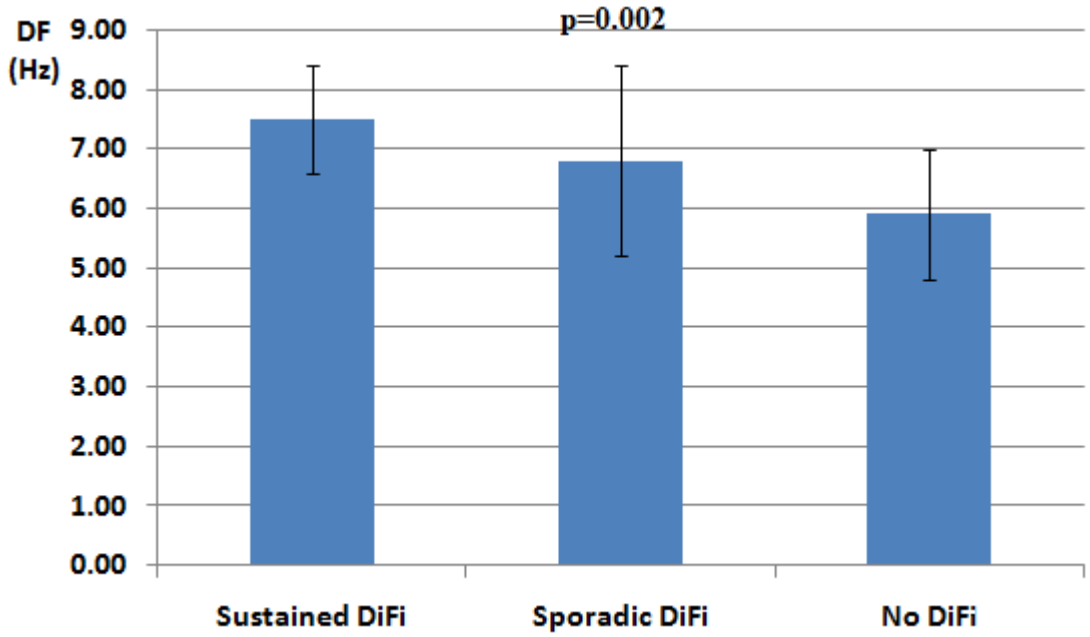

Figure 14. Dominant frequency (DF) during atrial fibrillation in PVs showing different types of dissociated firing (DiFi) after isolation

Clinical outcome

During the ablation procedure and a mean of 31±18 months of follow-up, no major complication occurred in any patient. Ten patients (32%) underwent a redo PVI procedure, and all of them had reconnected PVs which were reisolated. There was no difference in the redo rate between groups (29 vs. 35 %, p=0.690, for patients with and without DiFi, respectively).

Two patients (14%) with DiFi and seven patients (41%) without DiFi had a recurrence after the last procedure. One of the two patients with DiFi had asymptomatic recurrence and refused a second procedure. The difference in recurrence rate did not reach statistical significance (p=0.101).

However, patients with DiFi after PVI had a longer mean time to recurrent PAF after the last procedure compared to those without DiFi at the index procedure (52 vs. 32 months, p= 0.048) (Fig. 15).

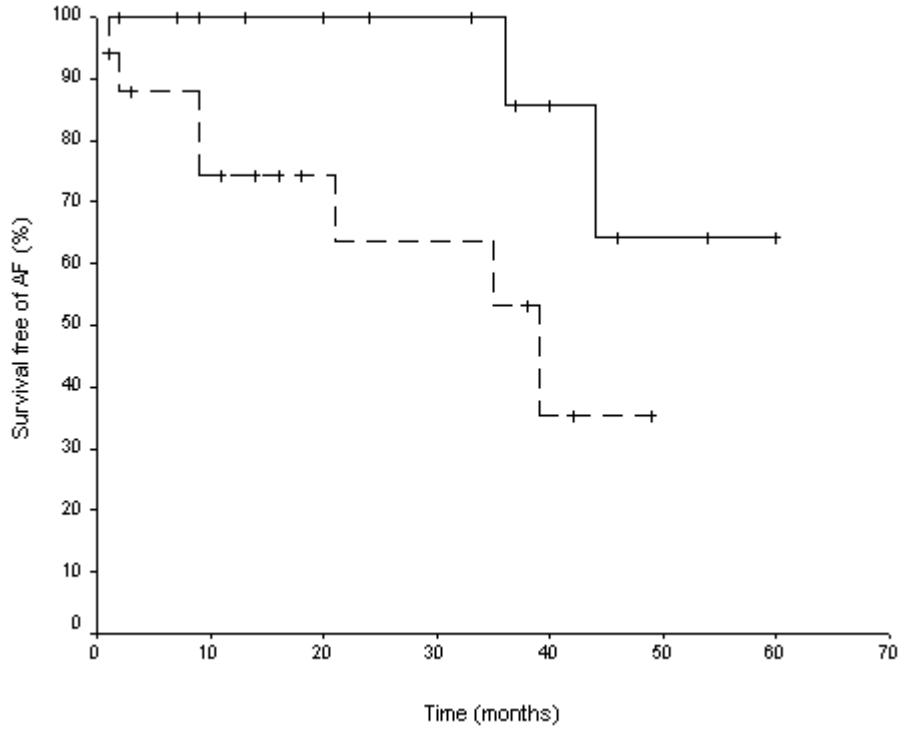

Figure 15. Kaplan-Meier curve of the freedom from arrhythmia recurrence. Patients with dissociated firing (DiFi) after PVI (continuous line) had a longer mean time to recurrence compared to those without DiFi (broken line)

Isoproterenol versus adenosine for the identification of atrial fibrillation triggers

Four (10%) patients from Study Group 3 could not receive any drug challenge because their spontaneous AF ongoing at the commencement of the procedure restarted immediately after DCCV. Eighteen of the remaining 36 patients were randomized to receive Iso first and 18 Ado first. In case of 10 (28%) patients the second drug was not given, because the AF induced by the first drug spontaneously restarted after DCCV. Therefore 36 (90%) patients received their first and 26/36 (72%) patients the second drug. Altogether 32 patients received Iso and 30 patients Ado (30 received 18 mg, 21 received 18 and 36 mg). AF was induced with Iso in 15/32 (47%) and with Ado in 12/30 (40%) patients (p=0.9). Iso-triggered AF started from the left PVs in 11 (73%), from the right PVs in 3 (20%), from the CS in 1 (7%) cases (Figure 16A). Ado-induced AF episodes originated from the left PVs in 6 (50%), from the RA in 4 (33%), from the CS in 2 (17%) cases (Figure 16B). Altogether Iso-induced AF was more likely initiated from the PVs (93%), compared to Ado (50%) (p=0.02).

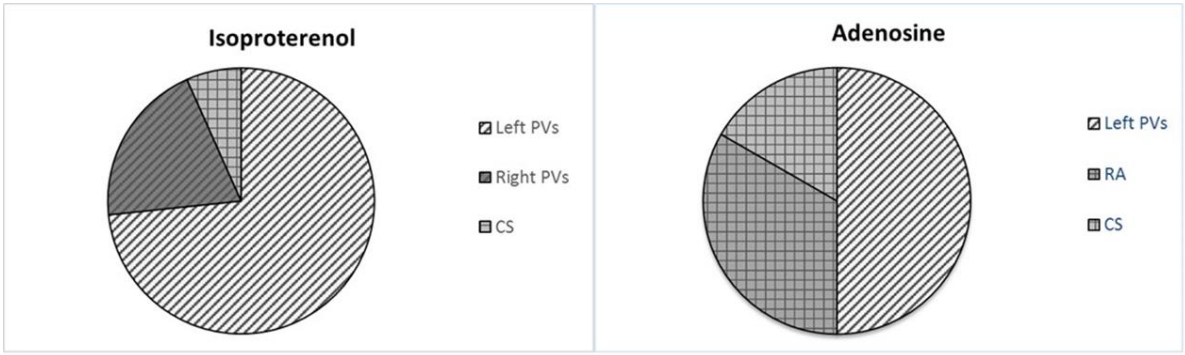

Figure 16. Trigger sites of isoproterenol induced AF (Panel A) and adenosine induced AF (Panel B).

Of the 26 (72%) patients (Figure 17, Table 3.) who received both drugs, AF could not be induced by drug challenge in 13 (50%). Iso triggered AF in 9/26 (35%) patients; all triggers were localized to the PVs (7 left, 2 right PVs). Ado was effective at inducing AF in 8/26 (31%), 2 from left PVs and 6 from non-PV sites (4 RA, 2 CS, $p<0.01$ versus Iso). Both drugs induced AF in 4/26 (15%) of these cases. In 2 of those 4 patients triggers originated from the left PVs with both Iso and Ado, while in the remaining two cases there was discordance between the two drugs, Ado manifesting non-PV triggers.

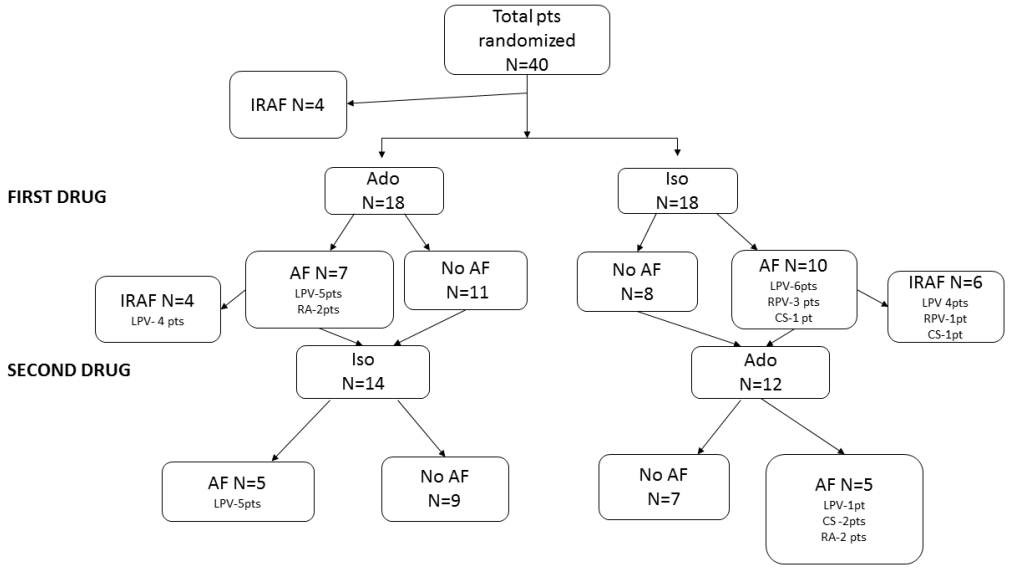

Figure 17. Study flowchart. IRAF: immediate recurrence of atrial fibrillation (AF) after cardioversion, Ado: adenosine, Iso: isoproterenol, LPV: left pulmonary veins (PV), RPV: right PV, RA: right atrium, CS: coronary sinus

Fourteen (35%) patients had spontaneous AF during the procedure, 13 (93%) originated from the PVs (9 left, 4 right PVs), and only one from the CS. Ten of these cases received one or both drugs. Iso reproduced left or right PV triggers in 6/7 cases and was ineffective in one. Ado reproduced left PV triggers in 4/7 cases, but was ineffective in 3. This results in a sensitivity to reproduce spontaneous triggers of 86% for Iso and 57% for Ado.

Patient #	First drug	Isoproterenol		Adenosine		Spontaneous triggers
		Max. dose (μg/min)	Induced triggers	Max. dose (mg)	Induced triggers	
1	Ado	10	LPV	18	RA	-
2	Ado	20	LPV	18	LPV	LPV
3	Iso	20	LPV	18	LPV	-
4	Iso	20	-	18	RA	-
5	Ado	20	-	18	RA	-
6	Ado	20	LPV	36	-	-
7	Ado	20	LPV	36	-	-
8	Iso	5	LPV	36	CS	-
9	Ado	20	LPV	36	-	-
10	Iso	15	RPV	36	-	RPV
11	Iso	3	LPV	36	-	LPV
12	Iso	20	-	36	-	-
13	Ado	20	-	36	-	-
14	Iso	20	-	36	-	-
15	Ado	20	-	36	-	LPV
16	Ado	20	-	36	-	-
17	Ado	20	-	36	-	-
18	Ado	20	-	36	-	-
19	Iso	20	-	36	-	-
20	Iso	20	-	36	-	-
21	Iso	20	-	36	-	-
22	Ado	20	-	36	-	-
23	Iso	20	-	36	CS	-
24	Ado	20	-	36	-	-
25	Iso	20	-	36	RA	-
26	Ado	20	-	36	-	-

Table 3. Characteristics of patients who received both drugs. Abbreviations are as on Figure 17.

After drug testing 38 of 40 (95%) patients underwent PVI. Two patients – for whom initially a selective PVI was planned - did not have an ablation (one was noninducible and one had RA trigger on Ado). Thirty of the remaining 38 (79%) received empirical isolation of all 4 PVs, while 8 (21%) patients a selective PVI of arrhythmogenic PVs. Ten of 38 (26%) underwent a second PVI procedure with the aim of 4-PV isolation, because of recurrence of AF. After the last procedure, 32 of 38 (84%) ablated patients were free of recurrence during 16±9 months of follow-up.

Of the 14 patients who had PV triggers disclosed by Iso infusion, one was lost to follow-up, and the rest had no AF recurrence after the last PVI. In case of the only patient with a non-PV trigger on Iso PVI was ineffective, even after a redo procedure. Among the 6 patients with PV triggers on Ado, PVI and redo PVI failed in one. Of the 6 patients with non-PV triggers on Ado, one was not ablated and one failed PVI and a redo. The remaining 4 are without recurrence after the last procedure. Therefore, while Iso was 100% accurate in predicting a favorable response to PVI, the accuracy of Ado challenge was only 55%. There was no correlation between non-PV triggers induced by Ado and arrhythmia recurrence after the last procedure ($p=0.90$).

DISCUSSION

During the last decade, numerous data became available regarding the long-term efficacy of the interventional treatment of atrial fibrillation. These data can be especially important for estimating prognosis, evaluation of currently available ablation techniques, and last but not least for the reimbursement policy of procedures.

To summarize the results of our literature review, we can conclude that long-term freedom from AF is achievable and maintainable over 2-3 years or even more with mild increases in arrhythmia recurrence over time. This statement is especially true for the paroxysmal AF population, following initial PVI procedures.

Single procedure success rate is definitely lower in the long-term, so for achieving a durable result, multiple procedures have to be taken into account. The success of an ablation procedure is less encouraging in the persistent population, moreover there is no real consensus regarding the best ablation strategy beyond PVI, to improve the long-term efficacy rate.

It is likely that the main mechanism behind very late recurrences of AF is the PV reconduction and recurrent PVs triggers, but progressive remodeling of left atrial substrate as well as non- PV triggers can play an important role over time, especially in the persistent AF population.

It should be noted that strict AF free success rates in both groups probably underestimate the real long-term clinical benefit of the procedures if we focus on symptomatic improvement or fewer hospitalizations.

Furthermore, it cannot be overemphasized that studies demonstrating very different results regarding the outcome of procedures are showing significant heterogeneity in terms of the definition of success, methodology of follow-up, and the applied ablation technologies.

One of the most important proarrhythmic complications after catheter ablation of AF is regular atrial tachycardia (AT) or flutter. ATs occur relatively frequently after AF ablation procedures.

The incidence of these tachycardias varies in the context of previous lesion set and probably of the extent of abnormal atrial electrophysiologic substrate. The mechanism in vast majority of cases is reentry related to gaps in prior ablation lines.

Conservative therapy is usually not effective; radiofrequency ablation procedure is mostly successful but can be challenging and requires a complex approach.

Left atrial mechanoelectric feedback

Understanding the pathophysiologic mechanisms that lead to AF initiation and persistence is very important in improving the outcome of the procedure. Atrial pressure elevation predisposes to atrial fibrillation by several mechanisms.

Acute atrial pressure increase leads to electrophysiologic changes, while chronic atrial stretch also induces structural remodeling. We have seen a dramatic fall in ERP and reservoir function in response to pressure rise in patients with AF, which did not happen in the normal LA. We conclude that the normal adaptation to acute elevations in LA pressure is lost in patients with AF, even during sustained sinus rhythm.

Even when in sinus rhythm, patients with paroxysmal AF show diminished LA reservoir function estimated by LA strain (77, 78). We have shown that LA strain is also dependent on LA pressure in patients with AF, and an acute rise in pressure leads to a decline in LA reservoir function and increased stiffness, a response not observed in the normal LA. In patients with paroxysmal AF, but without a recent episode, LA ERP measured at the LA appendage has been shown by some (79, 80), but not by other reports (81) to be longer than in controls, while it was consistently shorter in patients with persistent AF. The reason for this inconsistency might be the dependence of atrial refractoriness on pressure, a phenomenon known as mechanoelectric feedback (82).

Mechanoelectric feedback is well described in the ventricles, has been shown at the atrial level and in the human right atrium, but has not been studied in the human LA, the major source of AF (83-87). Acute atrial stretch increases vulnerability to AF in both animal models and humans (88, 89); the mechanism most commonly considered behind this is a shortening of refractoriness and slowing of impulse conduction (90-92), both promoting the development of reentry.

We have shown that pressure-related shortening of refractoriness-mechanoelectric feedback-is magnified in the LA of patients with AF, which likely facilitates the persistence of the arrhythmia. Paroxysmal AF itself leads to atrial pressure elevation (93).

According to our study, increased atrial pressure can result in increased stiffness and wall tension with shortened atrial refractoriness favoring AF maintenance. This way, a vicious circle is established, which may culminate in persistent AF. These results therefore suggest early intervention to prevent the progression of AF.

Dissociated firing (DiFi) from PVs

Trying to obtain a better outcome of PVI we searched if dissociated firing (DiFi) in isolated PVs implies arrhythmogenicity of the particular PV.

The main finding of our study is that PVs with DiFi after isolation show higher activation rate during fibrillation and, therefore, are more likely to have a role in the perpetuation of atrial fibrillation as compared to PVs without DiFi.

Furthermore, PVs showing DiFi more frequently initiate atrial fibrillation. Therefore, DiFi after PVI can be considered a hallmark of PV arrhythmogenicity pointing to the role of the particular PV both in the initiation and maintenance of PAF. When PAF is initiated and maintained by PV arrhythmogenicity rather than other mechanisms, PVI should have a better outcome.

Mechanism of DiFi

Spontaneous electrical activity of PVs after isolation presents as DiFi. It is either an escape rhythm overridden by the faster sinus node (SN) before isolation and unmasked by PVI or rapid ectopic triggering no longer capable of initiating PAF after isolation.

Specialized cells resembling those of the SN have been described in the PVs and are thought to be responsible for spontaneous automaticity (94-95) manifested as DiFi after PVI, which shows a pharmacological response similar to sinus rhythm (96).

However, PV electrical activity triggering PAF may have a mechanism that is different from the slow escape rhythm type of DiFi. Its mechanism is more compatible with triggered activity (97), being provoked by rapid pacing and the autonomic effects of adenosine (98), rather than being suppressed. This type of activity most commonly is eliminated by circumferential ablation around the PVs, possibly due to the effects of ablation on the autonomic nervous system (99). Therefore, the association between DiFi and PV arrhythmogenicity deserves further investigation.

Incidence of DiFi after PVI

The incidence of DiFi after PVI shows a broad variation from 2.8 to 92% (96, 100). This variation may be explained by differences in the definition of dissociated activity, study population, or ablation approach. Kabra et al. (100) reported an incidence of 92% of DiFi after PVI for PAF, and similar to our study, the DiFi was classified as isolated ectopic beats, ectopic regular rhythm, or PV fibrillation.

In contrast, Buiatti et al. (101) in a recent study reported that 27% of their patients had at least one vein (12% of PVs) with DiFi, but the investigators took a unique approach to define the dissociated activity (slow intermittent potentials without a regular rhythm) and excluded most of what we have defined as DiFi.

In our study, the incidence of DiFi was 45% of PAF patients presenting for PVI. Consistent with a previous study (102), we observed a higher proportion of DiFi originating from superior PVs compared to inferior veins.

Also, PAF was triggered most commonly from upper PVs, similar to previous reports (103). This may be related to thicker muscle sleeves (104) Guerra et al. (105) linked areas of PV wall thickening to high-frequency potentials and the origin of ectopic beats.

We could not find any significant correlation between the size of PVs and the presence of dissociated activity after isolation. The ablation technique also has an impact on the occurrence of DiFi after PVI.

Segmental, ostial isolation resulted in a DiFi rate of 5-33% (106), while wide-area encircling ablation resulted in up to 85-92% (100, 106, 107). This suggests that ablation closer to or inside the PV ostium (e.g., at the carina) can destroy some of the foci responsible for DiFi.

Prognostic implications of DiFi

Similar to the above mentioned reports defining the incidence and characteristics of DiFi, studies on the impact of dissociated activity on the outcome of PVI are also conflicting. Some have shown improved outcome of PVI in patients with DiFi (108, 109)and better success rate when the foci of DiFi were ablated inside the PVI lesions, rather than left untouched.

However, others have reported either no difference (101, 102, 110) or even increased recurrence rate in the case of DiFi that is not ablated (111).

The explanation for an improved success rate in the aforementioned studies is either that DiFi is a marker of more proximal and better quality ablation lesions, providing evidence of exit block from the PVs (8) or that DiFi is a marker of PV arrhythmogenicity (7).

Relation between DiFi and PV arrhythmogenicity

Although, in two previous studies, the association between triggering PVs and DiFi was assessed (101,108), a systematic approach to PAF induction was not employed and the proportion of patients with the triggering structure identified was low (10 and 44.5%, respectively). Furthermore, the definition of triggering and DiFi was variable. One of these

studies (101) suggested an association between PVs with PAF triggers and DiFi, while in the other, it was not significant (108).

We included only patients with the triggering PV identified (defined as the vein from which ectopic activity initiated PAF) and observed a significantly higher incidence of DiFi after isolation of a triggering PV, compared to nontriggering ones. This suggests that PVs with DiFi after PVI are more likely to have a role as initiators of PAF. We previously described (73) that triggering PVs showed the fastest activity during sustained PAF, pointing to their role not only in the initiation but also in the perpetuation of the arrhythmia.

In this study, we observed that PVs with DiFi showed faster maximal DF during PAF compared to PVs without DiFi, suggesting an association between DiFi and the maintenance of PAF. In addition, the correlation between DiFi and arrhythmogenicity of a PV both as initiator and perpetuator of PAF became more pronounced with more expressed (sustained vs. sporadic) DiFi. In line with the above and similar to studies showing DiFi to be a positive predictor of success (7, 8), we found that patients with DiFi after PVI had a longer mean time to recurrent PAF compared to those without DiFi.

These results confirm that observing DiFi from isolated PVs is related to the arrhythmogenicity of the PV. The presence of DiFi is associated with a better outcome of PVI not because the quality of PVI is higher but because it implies that PAF is more likely to have a PV-based mechanism for the particular patient. On the contrary, patients without DiFi after PVI are more likely to have non-PV mechanisms and more advanced atrial substrate involved in the arrhythmia. This is further supported by previous studies finding more structural heart disease (6, 110), hypertension (7), and non-paroxysmal atrial fibrillation (110) among cases without DiFi and a trend for a lower left ventricular ejection fraction in our study.

Induction of AF triggers in the electrophysiology lab

AF catheter ablation can be more successful by identifying and eliminating sites that can trigger paroxysmal and persistent AF. Identification and ablation of non PV triggers after PVI has been associated with improved arrhythmia free survival. Besides isoprenaline (Iso), adenosine (Ado) can be used for the induction of atrial fibrillation (AF) during electrophysiology studies, however data are lacking on the sensitivity and specificity of Ado-challenge. The main finding of our study is that, while Iso mostly induces PV triggers, Ado is more likely to induce non-PV triggers of AF, dominantly from the RA. Half of Ado-inducible patients had AF from non-PV sites, compared with only 7% with Iso. Moreover, in two cases

the two drugs showed divergent effects in the same patient: Ado inducing non-PV, while Iso PV triggers.

While trigger sites disclosed by Iso challenge showed excellent correlation with the long-term response to PVI (no recurrence in case of PV triggers and recurrence in the single case of non-PV trigger), there was no such correlation seen with Ado, PVI being equally effective in those with PV or non-PV triggers induced by this drug.

Comparison with previous studies

The use of Iso in the electrophysiology lab to study triggers of AF is well established (12, 13). It has been shown to effectively identify arrhythmogenic PVs that can selectively be ablated, achieving similar success to empirical 4-PV isolation (112). On the other hand, Ado has mostly been used anecdotally for AF induction. A number of case reports have been published of triggers identified with Ado or ATP, most of which originated outside the PVs (113-118). More investigators have used ATP to test for non-PV triggers after PVI (119-121). Strikingly most of these studies originate from Asia, utilize ATP, and report a high rate of non-PV triggers (122).

Tao et al. (123) used adenosine-triphosphate (ATP) 20 mg for induction in patients with paroxysmal or persistent AF. They found that ATP induced AF in 30% of the cases and trigger sites were from the PVs in more than 80% of these. The higher rate of PV-triggering with ATP compared with our results with Ado may be explained by differences in the mode of action and relative doses of the two drugs. The molecular weight of ATP is approximately twice that of Ado; therefore, the number of adenosine molecules in 20 mg ATP is much less than in 18 mg of Ado, the lower dose in our study.

On the other hand, ATP exerts a much more pronounced negative chrono- and dromotropic response due to its action on P2 receptors located in the left ventricle inducing a cardiocardiac vagal reflex (124). The higher relative dose and exclusive action on adenosine (P1) receptors may explain the higher rate of RA triggers we saw with Ado.

Nevertheless, another report from Japan using ATP showed a higher rate of RA triggers. Hasebe et al. (125) also used 20 mg of ATP after other methods of AF induction, including Iso, failed. More patients had RA triggers than PV triggers with ATP injection (6 vs. 4) and frequency analysis suggested the driver to reside in the RA during AF in those with RA triggers. These patients were younger and also more often had a family history of AF. The authors suggested they may have a distinct form of the arrhythmia, which they named RA

fibrillation. However, it is possible that in Hasebe's study (125), younger patients were more difficult to induce with other methods (including Iso) and therefore more likely to receive ATP or Ado. The higher rate of RA fibrillation in their case might be merely a manifestation of the preferential effect of ATP/Ado on the RA. (125)

The high percentage of RA triggers seen with Ado/ATP may be related to the drug's route of administration, short half-life and mode of action. Ado/ATP is administered into a central vein or directly the RA, and therefore the concentration of the drug is higher in the RA than the LA, after having travelled through the lungs, where – due to its very short half-life – a great fraction may be eliminated. Moreover, the sensitivity of the RA to Ado is known to be higher than the LA (126, 127), explained by an at least two-fold higher expression of the Ado receptor in the RA (128). Receptor density in the RA has also been correlated to Ado-induced AF in humans (128). Although direct injection of adenosine into the LA had been proposed, this was not done in our study, due to concerns of air embolism (129).

Relation between induced and spontaneous triggers

Few studies have compared induced and spontaneous AF. Lazar et al. analyzed atrial activation frequency distribution and found no difference between patients with spontaneous AF (3 patients) and Iso-induced AF (13 patients) (130), while Calvo et al. showed the same for pacing induced AF (131). In the abovementioned study, Tao et al. (123) found that the spontaneous AF initiation site was in the PVs in 96% of cases, while after ATP injection in 85%.

Only in one of the 4 patients with a non-PV trigger manifested by ATP was there a correlation with the spontaneous site. In other words, they show - similarly to our results - more non-PV triggers with ATP, compared with spontaneous AF, but the majority of those ATP-induced non-PV triggers were not clinical. We have seen 4 patients in whom Ado reproduced spontaneous AF, but none originated outside the PVs. Therefore, it seems that Ado/ATP may reproduce PV-triggers; however, the frequent non-PV triggers seen with these drugs cannot be correlated with spontaneous AF.

The question arises whether non-PV triggers induced by Ado are clinically relevant as initiators of spontaneous AF. Triggers of spontaneous AF in our and the above mentioned reports (11, 12, 111) have been located to the PVs in more than 90% of the cases. The high percentage of non-PV AF-initiating sites seen with Ado is in sharp contrast with this observation.

CONCLUSION

Atrial fibrillation (AF) is an arrhythmia of increasing prevalence. Catheter ablation is an important therapeutic modality for the treatment of patients with AF. Despite a continuous improvement in knowledge and technology of PVI is still associated with significant recurrence rate especially in persistent AF. Improvement in the outcome of the procedure can be expected by influencing the mechanisms leading to persistence of AF, like mechanoelectric feedback.

Better identification of the structures responsible for arrhythmia initiation and maintenance by drug challenge and monitoring for DiFi, meticulous care in isolation of arrhythmogenic PVs, as well as ablation of non-PV triggers can also improve therapeutic efficiency.

However, it should be kept in mind that adenosine is likely to induce non-PV triggers without established clinical significance and therefore cannot be recommended for the identification of trigger sites to guide catheter ablation of paroxysmal AF.

NEW OBSERVATIONS

1. The normal LA can adapt to episodes of acute pressure elevation without a substantial change in reservoir function and ERP. On the other hand, patients with AF show an exaggerated fall in LA reservoir function in response to pressure rise, with an out of proportion increase in wall tension leading to a decline in LA ERP. This mechanoelectric feedback likely further promotes the development of AF.
2. Pulmonary veins with dissociated firing are more likely to have a role as initiators and perpetuators of paroxysmal AF.
3. Adenosine is much more likely, than isoproterenol to induce non-PV triggers, especially from the RA. The clinical significance of these foci, however, is questionable therefore it cannot be recommended for the identification AF triggers.

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ACKNOWLEDGEMENT

First of all, I would like to say a very big thank you to my supervisor, Dr Pap Robert, for all the support, encouragement and advice he has provided throughout my time as his PhD fellow. Without his guidance and constant feedback this PhD would not have been achievable.

Apart from my Supervisor, I won't forget to express the gratitude to Dr Laszlo Saghy, who have provided me with the opportunity to perform my work in Szeged EP departments.

I would especially like to thank my colleagues and all nurses from the EP lab. Without they precious support it would not be possible to conduct this research.

Last but not least, I would like to express my deepest gratitude to my husband. This dissertation would not have been possible without his continued patience, and endless support.

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Very Long-Term Results Of Atrial Fibrillation Ablation Confirm That This Therapy Is Really Effective

Cristina Tutuianu, MD, Judit Szilagy MD, Robert Pap, MD, PhD and László Sághy, MD, PhD.

2nd Department of Medicine and Cardiology Center, Electrophysiology Division, University of Szeged, Szeged Hungary

Abstract

Catheter ablation -in general- is a highly effective and "curative" intervention for a broad spectrum of supraventricular and ventricular arrhythmias. After a successful procedure eliminating a simple arrhythmia substrate, the recurrence rate is low and the short term success correlates well with the long term freedom from the arrhythmia.

Introduction

Since the identification of trigger activity in the pulmonary vein by Haissaguerre et al,[2] catheter ablation of atrial fibrillation (AF) has became an established therapeutic modality for the treatment of patients with AF. Published data in the literature suggest that success rates following ablation of AF are relatively favorable (50-70%)[3,4,5] but most studies have reported limited follow-up of 1 or 2 years after the first ablation and the long-term outcomes have not been fully elucidated.

Why do we need more information regarding the long term follow up data following AF ablation, in contrast with conventional ablation procedures?

First, the clinical significance of an AF recurrence is usually more pronounced than other arrhythmias because of the well known deleterious consequences of this arrhythmia, with special attention to thromboembolic complications.

Furthermore, the pathologic mechanism of AF is complex with a special interplay between the triggering structures and a continuously evolving left atrial substrate. Consequently, it is important to analyze the long term response and define the durability of different ablation techniques to achieve a better clinical outcome.

Pulmonary vein isolation (PVI) is the mainstay therapy of paroxysmal AF, but its success is suboptimal in the persistent population.[5,6] Additional ablation techniques have been introduced during the last decade.[5] The AF population is very heterogeneous, with respect to duration and type of arrhythmia, comorbidities etc. On top of that, ablation results may depend on different definition of success, and follow up methods. Consequently, a comprehensive discussion of long term outcome of catheter ablation should include parameters like type of AF, ablation strategies, the use of antiarrhythmic drugs after ablation, multiple procedures, success definitions, the frequency and intensity of arrhythmia monitoring. The aim of the current study is to review the literature and evaluate the very long term success of catheter ablation of AF.

Disclosures:
None.

Corresponding Author:
Dr. Tutuianu Cristina,
2nd Department of Medicine and Cardiology Center,
Electrophysiology Division,
University of Szeged, Szeged Hungary.

Definition Of Long Term Follow Up

In the 2012 Expert Consensus on catheter ablation of atrial fibrillation,[7] late recurrence of AF is defined as a recurrence after 12 months or more after AF ablation and the long term success is defined as freedom from AF following the 3 months blanking period through a minimum of 36 months There is also consensus that all patients who undergo catheter ablation of AF should be controlled every six months for at least two years. In our review, we defined very long term follow up to be longer than 3 years after the index procedure

Impact Of Type Of AF

Depending on whether patients have paroxysmal (PAF), persistent, or longstanding persistent AF, the outcome of ablation procedures differs considerably. A systematic review and meta-analysis including17, mostly retrospective studies published by Ganesan et al[8] demonstrated that the single procedure success for PAF was 68.6 % at 1 year, 61.1% at 3 years and 62.3% at 5 years. After multiple procedures (average 1.45 procedure per patient) 79% of patients were free from AF at 5 years follow-up. Comparing patients with persistent and long-standing persistent AF after a single procedure the results were less favorable, 50.8% at 1 year, and 41.6% at 3 years. After multiple procedures, the success was definitely more promising in this population, 77.8 % in the long term, but only few studies reported the outcome of AF ablation after more than 3 years suggesting that we need more data to definitively assess the very long term efficacy

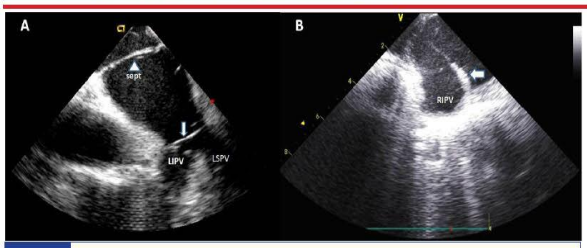

Figure 1: **Antral isolation of the left and right pulmonary veins guided by intracardiac echocardiography. Panel A: Lasso catheter was placed in the left common ostium between the left inferior and superior pulmonary vein (white arrow). Panel B: Ablation catheter (white arrow) is touching the right venous carina next to the right inferior pulmonary vein. LSPV: left superior pulmonary vein, LIPV: left inferior pulmonary vein, RIPV: right inferior pulmonary vein, Sept: interatrial septum. Images are originating from the database of Szeged University.**

of ablation in persistent atrial fibrillation. The authors concluded that both single and multiple procedure success rates showed adequate stability over 3 years with a significant residual risk for a recurrence and the paroxysmal cohort demonstrated a superior single procedure efficacy. Tzou et al[9] reported an AF freedom, off AAD, of 85% at 3 years and 71% at 5 years, with a 7% per year late recurrence after the first ablation in a mixed paroxysmal and persistent AF population. In a multivariate analysis, persistent AF was an independent predictor for recurrence.

Recently, Steinberg et al.[10] published a large prospective cohort of AF population (72% paroxysmal, 28 % persistent) and followed 445 patients for even a decade after a 1 year complete success following PVI. During a 62 months median follow up, 22 % of patients developed very late arrhythmia recurrence, and the authors demonstrated that the slope of the recurrence curve declined linearly. When they analyzed the differences in outcome on the basis of the arrhythmia pattern before the index ablation procedure, the results were strikingly different. The recurrence rates at 2, 5, an 10 years were 3%, 11%, and 27 % vs 13%, 29%, and 62% for paroxysmal and persistent AF patients, respectively (P< .0001). The authors concluded that the majority of AF patients did quite well over the time, and the ablation results are sustainable even for the long term as well, but using multivariate analysis, persistent AF (hazard ratio 3.08; P< .0001) was an independent risk factor for recurrence of AF.

An interesting question concerning the long term recurrence and efficacy of the ablation procedure whether these interventions can prevent progression of the arrhythmia from paroxysmal to persistent form. In the study of Takigawa et al[3] during a median follow up of approximately 48 months, AF progressed from paroxysmal to persistent in 1.2 % of patients in accordance with previous investigations where the AF progression rate was similar (1.5% -3%).[11,12] In contrast, the results of pharmacologic therapy are definitely worse, the reported rates vary between 5.5% and 15%/year.[13,14] These observations suggest that the interventional therapy is better than drugs alone for preventing AF progression, which is an important aspect of long term consequences of the arrhythmia.

Impact of Ablation Techniques

Whereas a consensus has been reached on the suitable approach for ablation of patients with paroxysmal AF,[7] no such consensus exists for patients with persistent and long lasting persistent AF regarding the optimal technology of treatment.

Numerous clinical trials demonstrated that the main mechanism of AF recurrence after PVI in the paroxysmal population is the resumption of electrical conduction between the veins and left atrial muscle. This statement is true for either the short or the long term recurrences (see below).[8,15] Based upon these observations we should assume that at least in PAF, the durability of venous isolation and therefore permanent electrical disconnection plays a crucial role in maintaining procedural effectiveness in the long term. Accordingly, any kind of procedural tool or technique which can facilitate the durable isolation of pulmonary veins can be useful.

Segmental PV ablation or wider continuous circumferential antral ablation, two different procedures which have been used most commonly in clinical practice showed different outcomes. Sawhney et al[16] reported that 86% of the patients were free from AF at 1 year follow up after segmental pulmonary vein isolation, with 79%, and 56% free at 2 and 5 years respectively. A meta-analysis done by Proietti at al[17] including 12 studies that compared the effectiveness of wide antral versus segmental pulmonary vein isolation concluded that PVI performed with a wide antral approach is more effective than ostial PVI in achieving freedom from atrial tachyarrhythmia recurrence at long-term follow-up (OR, 0.33; 95% CI, 0.24-0.46; P< .00001). They excluded the studies in which electric isolation was not assessed or if different catheter technologies were used. Ganesan et al[8] also investigated if there is a statistical difference in outcomes of segmental PV isolation compared with wide antral circumferential ablation. The conclusion here was no, but they included also the studies with wide circumferential ablation without assessing the isolation of the pulmonary veins.

An alternative energy source that has been developed to overcome some of the disadvantages of radiofrequency ablation is cryoenergy using a balloon based technology. A comparison (1:1 propensity score match) between cryoballoon and radiofrequency ablation showed similar long term success rates with a recurrence rate of 45 % in both groups after a two-year follow-up.[18] Neumann et al[19] reported freedom from AF in 74% of patients with paroxysmal AF and 42% with persistent AF, but the follow up time was shorter. Cryoablation is a new technology and it is under continuous development, but whether it can improve very long term outcomes has to be investigated in the future.

As mentioned earlier, in patients with persistent and longstanding persistent AF the data concerning the outcomes are considerably less favorable than for PAF. The wide contrast in PVI success rates between paroxysmal and persistent AF suggested that the mechanisms can be substantially different, and probably related to electrophysiological and structural remodeling of left atrial substrate. Not surprisingly,

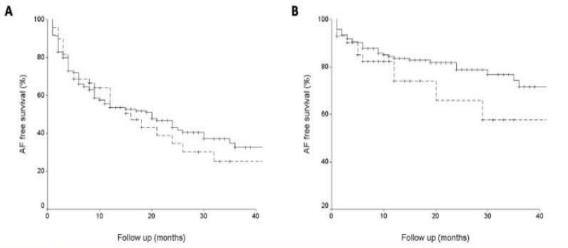

Figure 2: **Kaplan-Meier curve representing the arrhythmia free survival after single ablation procedure (Panel A) and following multiple ablation procedures (Panel B) in patients with paroxysmal (solid lines) vs persistent atrial fibrillation (broken lines). Data are originating from the database of Szeged University**

current approaches designed to target persistent AF are mainly based on modification of the atrial substrate, but exhibit remarkable differences, and a widely accepted uniform strategy is missing.

Different ablation strategies, including the ablation of complex fractionated atrial electrograms (CFAEs),[20] linear lesions in the left atrium,[21] ablation at the maximal high dominant frequency spots,[22] rotor ablation[23] have been developed as an add-on to pulmonary vein isolation to improve the outcome in this group. PVI alone can be sufficient to maintain sinus rhythm in 21% of patients after a single procedure and in 43.2% after 1-3 procedures in a retrospective analysis.[6] The same 21-22% success with a single procedure and 37-43% success rate after repeat procedures was published by Brooks at al[5] in a review of 32 studies. They also reported the success rate of other techniques: linear ablation in addition to PVI (11-74%), posterior wall isolation (42-50%) CFAE ablation (36-68%) or "stepwise" ablation approach (38-62%). The integration of repeat procedures and addition of previously ineffective antiarrhythmic drugs further improved clinical success. The variation in the success rate suggests that the best approach in this group is still unclear. However, persistent and long-standing persistent AF can be treated with a relatively high success rate during rather a medium term follow up, since really long term data are still lacking.

Our approach is wide area antral circumferential ablation for paroxysmal and persistent patients as well, with complete isolation of pulmonary veins, without creating additional lesions in the left atrium. During the procedures we use open irrigation radiofrequency catheters and a combination of EAM and intracardiac echocardiography (Figure 1) to enhance the anatomical orientation and the monitoring of catheter-tissue contact. After a mean of 18 months follow up time the recurrence rate after single procedure was 52% and 61%, after multiple procedures was 19% and 29%, in a paroxysmal and persistent cohort respectively (Figure 2).

Impact of Follow up Techniques

Apart from the above mentioned factors, the varying results reported by those studies could be attributed to substantial differences in follow up methods. During the first year, the majority of studies performed clinical examination, electrocardiogram and 24-hour Holter monitoring or event recorders at 3, 6, and 12 months. Beyond the first year, the intensity of follow up is usually reduced to 1 or 2 outpatient visits per year or even based on data from referring clinicians.[24] There is a clear positive correlation between the duration and intensity of the follow-up and the arrhythmia detection rate.[25] For the short term follow up, 7 day Holter and transtelephonic monitoring are proven to be effective to detect asymptomatic AF episodes. Piorkowski et al.[25] showed that using serial 7 day Holter and transtelephonic monitoring, the „real" procedural success rate decreased from 70% to 50% and 45 % respectively.

The definition of long term ablation success remains controversial because current post ablation rhythm monitoring strategies are based on symptom and/or intermittent ECG recordings and thus probably underestimate the real rate of AF recurrences.[26] Continuous monitoring like implantable loop recorders are useful tools[27] but to put these devices into an everyday practice is limited by cost, patients compliance and high burden of false detection.

Predictors And Mechanism Of Recurrence

As we suggested earlier, the success of catheter ablation may depend on technical aspects of the procedure but also on patient related factors. Patients in whom AF recurred, exhibit specific clinical characteristics which can be considered as independent predictors of late AF recurrence. Some studies reported history of persistent AF as a predictor of very late recurrence[8,9,10] while other studies found that there was no significant association between the AF type and risk of recurrence.[15,28] The heterogeneity in results across the studies can be explained by the heterogeneous definition of AF type and the differences in terminology pertaining to "long term" follow up. The duration of AF history is a very important predictor of AF recurrence,[3] but other studies could not find a significant association between AF duration and AF recurrence.[29,30] A possible explanation is that duration of AF does not necessarily correlate with the length of the AF episodes and may not reflect the extent of atrial remodeling.[31] Other commonly identified predictors of AF recurrence are age > 65 years, left atrial diameter >24mm/m^2,[31] left ventricular systolic dysfunction, heart failure, structural or valvular heart disease,8 hypertension and hyperlipidemia.[15] These observations indicate the role of enhanced vulnerability of left atrial myocardium induced by these factors beyond the importance of trigger mechanism. Aggressive medical treatment of these conditions and risk factors reduction[32] may improve the efficacy of AF ablation. Pathak et al[32] reported in a recent publication that risk factor management according to American Heart Association/American College of Cardiology guidelines significantly improved the outcome of AF ablation in terms of AF burden and also generated favorable changes in cardiac remodeling.

The main mechanism of the early recurrence following atrial fibrillation ablation is the reconnection of previously isolated pulmonary veins. In contrast, in patients with very late recurrence the mechanism is not completely elucidated. Lin et al[33] found that the majority of patients with recurrent AF undergoing a 3rd or more procedure after a mean follow up of 36±22 months (range 12 to 119 months) had reconnected pulmonary veins with triggers originating from the culprit PVs. (Figure 3). However, in 20% of patients, new non-PV triggers were identified at the time of 3rd or 4th procedure

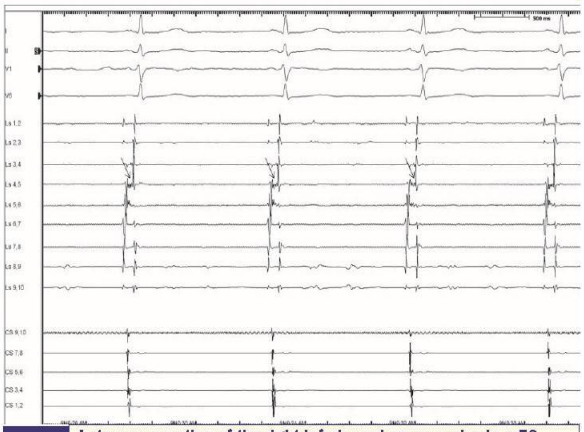

Figure 3: **Late reconnection of the right inferior pulmonary veins in a 56 years old patient with PAF following 32 months the index PVI. Single ablation attempt at the level of earliest PV potentials on Lasso,[4-5] bipoles (arrow) resulted immediate isolation of the vein. All of the other pulmonary veins were isolated. Surface ECG leads I, II, V1 and V6, together with intracardiac recordings from the Lasso catheter (Lasso) placed in the right inferior pulmonary vein, and from the proximal to distal coronary sinus bipoles (CS). Tracing is originating from the database of Szeged University.**

and the majority of non-PV triggers were mapped in the right atrium or coronary sinus. Steinberg at al[10] also found that in patients undergoing reablation for very late AF recurrence, just 4% of PVs were completely isolated. Conversely, Sotomi at al[34] found that the prevalence of PV reconnections and trigger PV reconnection were significantly lower in the very late recurrence group (>12 months, 69%) than in the late recurrence group (3-12 months, 90%) and also more patients required non-PV trigger ablation. In accordance with this observation, Kurotobi at al[35] demonstrated that the presence of residual arrhytmogenic non-PV foci are associated with an increased long term recurrence rate after successful isolation of PVs and left atrial linear lesions in a long-standing persistent AF population.

Conclusions

During the last decade, numerous data became available regarding the long term efficacy of the interventional treatment of atrial fibrillation. These data can be especially important for estimating prognosis, evaluation of currently available ablation techniques, and last but not least for the reimbursement policy of procedures. If we summarize the results of mostly retrospective analyses, we can conclude that long term freedom from AF is achievable and maintainable over 2-3 years or even more with mild increases in arrhythmia recurrence over the time. This statement is especially true for the paroxysmal AF population, following initial PVI procedures. Single procedure success rate is definitely lower in the long term, so for achieving a durable result, multiple procedures have to be taken into account. The success of an ablation procedure is less encouraging in the persistent population, moreover there is no real consensus regarding the best ablation strategy beyond PVI, to improve the long term efficacy rate.

It is likely that the main mechanism behind very late recurrences of AF is the PV reconduction and recurrent pulmonary vein triggers, but progressive remodeling of left atrial substrate as well as non-PV triggers can play an important role over time, especially in the persistent AF population.

It should be noted that strict AF free success rates in both groups probably underestimate the real long term clinical benefit of the procedures if we focus on symptomatic improvement or fewer hospitalizations. Furthermore, it can not be overemphasized that studies demonstrating very different results regarding the outcome of procedures are showing significant heterogeneity in terms of the definition of success, methodology of follow up, and the applied ablation technologies.

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Current Cardiology Reviews, 2015, *11*, 149-156

Atrial Tachycardias Following Atrial Fibrillation Ablation

László Sághy*, Cristina Tutuianu and Judith Szilágyi

2nd Department of Internal Medicine and Cardiology Centre, University of Szeged, Korányi fasor 6. 6724 Szeged, Hungary

Abstract: One of the most important proarrhythmic complications after left atrial (LA) ablation is regular atrial tachycardia (AT) or flutter. Those tachycardias that occur after atrial fibrillation (AF) ablation can cause even more severe symptoms than those from the original arrhythmia prior to the index ablation procedure since they are often incessant and associated with rapid ventricular response. Depending on the method and extent of LA ablation and on the electrophysiological properties of underlying LA substrate, the reported incidence of late ATs is variable. To establish the exact mechanism of these tachycardias can be difficult and controversial but correlates with the ablation technique and in the vast majority of cases the mechanism is reentry related to gaps in prior ablation lines. When tachycardias occur, conservative therapy usually is not effective, radiofrequency ablation procedure is mostly successful, but can be challenging, and requires a complex approach.

Keywords: Atrial fibrillation ablation, pulmonary vein isolation, atrial tachycardia, peri-mitral flutter.

INTRODUCTION

Over the last decades, pulmonary vein isolation (PVI) has become the mainstay of ablation treatment of paroxysmal atrial fibrillation (AF), however the success rate of PVI alone remained suboptimal in the persistent AF population. This observation has led to the development of adjunctive ablation strategies targeting the left atrial (LA) substrate itself, creating linear radiofrequency (RF) lesions or eliminating complex fractionated left atrial electrograms (CFAE).

Regardless of the ablation techniques used, RF ablation of AF may result in regular atrial tachycardias (ATs) or flutter, which is one of the most important proarrhythmic complications after LA ablation.

Atrial tachycardias that occur after AF ablation can cause even more severe symptoms than those from the original arrhythmia prior to the index ablation procedure since they are often incessant and associated with rapid ventricular response, which is difficult to control using antiarrhythmic medications.

INCIDENCE

Depending on the method and extent of left atrial ablation and on the electrophysiological properties of underlying LA substrate, the reported incidence of late ATs is variable. The less is the harm caused in the LA, the lower is the incidence of late AT. Consequently using the "initial" approach of segmental electrical PVI, which is limited to the ostia of pulmonary veins (PV) the occurrence was found to be relatively low, between 1% and 2.9% [1-3]. Oral *et al.* [4] demonstrated in a prospective randomized study that in patients with symptomatic paroxysmal atrial fibrillation LA ablation to encircle the pulmonary veins is more effective than segmental ostial catheter ablation in terms of freedom from symptoms. Also Gaita *et al.* [5] concluded that in persistent atrial fibrillation, pulmonary vein isolation plus left atrial linear lesion is superior to pulmonary vein isolation alone in maintaining sinus rhythm. However, when PV ablation was achieved by placing circular lesions around the veins in the LA antrum, without targeting complete isolation of pulmonary veins, and creating additional lines in LA (e.g. mitral isthmus, and/or roof, or posterior lines) the incidence of ATs dramatically increased to even 10 fold higher, ranging from 10% to 24 %, [6, 7].

Karch *et al.* [8] conducted a randomized study to compare segmental pulmonary vein ablation approach, which electrically isolates the pulmonary veins to circumferential pulmonary vein ablation approach plus creating linear lesions in the left atrial myocardium, without isolation of veins or electrical completeness of lines. Atypical flutter was observed in 18% of patients after circumferential ablation versus 2% ($p<0.001$) after complete isolation of veins, which drew the attention to the importance of incomplete lines in arrhythmogenesis. In accordance with this observation, Sawhney *et al.* [9] randomized a series of patients with structurally normal hearts and paroxysmal AF to PVI with electrical isolation versus circular PV ablation plus additional lines with confirmation of completeness of circular and linear lines. After isolation of PVs without additional lines there were no cases with left ATs, but 24% had AT in the other group, despite having originally complete lines, without difference in AF recurrence rate. The authors concluded that in patients without structural heart disease linear ablation should be avoided as an initial ablation approach.

*Address correspondence to this author at the 2nd Department of Internal Medicine and Cardiology Centre, University of Szeged, Korányi fasor 6. 6724 Szeged, Hungary; Tel: +3662545820; Fax: +3662545236; E-mail: saghylaszlo@hotmail.com

1875-6557/15 $58.00+.00

Nademanee [10] was the first, who reported a different approach focusing on complex fractionated atrial electrograms (CFAE) as a target of ablation procedure mainly in persistent AF population. The incidence of LA AT was 8 %. Later, Estner and co-authors demonstrated in their randomized study [11] that comparing PVI plus linear lesions or PVI plus additional CFAE ablation-so called "spot ablation"-the overall recurrence rate was similar, but the mode of recurrence was different: regular AT was the prevailing type of arrhythmia in the spot ablation group (11 vs. 29%, p=0.03). Furthermore, Rostock *et al*, [12] published a stepwise approach of persistent atrial fibrillation, including PVI and extended lesions in left and right atrium. Following this strategy, 40% of patients developed ATs during the follow up.

Relatively few data is available in the literature regarding the incidence of LA ATs after antral PVI exclusively, in the absence of additional lines or ablation of CFAE. Our approach is the wide area circumferential antral PVI for treating patients suffering mainly from paroxysmal AF, using CT or MR image integration as well as intracardiac echocardiography (Fig. **1**). The prevalence of left atrial AT is 11 % in our population which is more common than in the study by Wasmer *et al*. [13], who published a 4 % incidence in a very similar cohort recently.

Organized ATs most commonly occurred several weeks to months after the AF ablation procedure, 8.8±7.7 months in our population, but sometimes during the initial attempt (either spontaneously or induced). Regarding the ATs induced immediately after the AF ablation the reported incidence was observed between 16%-36% [7, 14, 15]. One of these trials demonstrated that AT during the initial procedure was an independent predictor for an occurrence of late AT. Chang *et al*. showed [15] that elimination of all inducible ATs during the index procedure can decrease the incidence of late ATs (0.6%), suggesting that non-inducibility of AT can be an ablation endpoint. However, in contrast with this statement, other authors suggested that the mechanism of acute ATs is different from that of late ATs and may represent focal drivers that become manifest after elimination of higher frequencies and fibrillatory conduction in persistent AF population [16].

MECHANISM

Focal AT

The mechanism of atrial tachycardia varies with the ablation technique and to establish the exact mechanism of these tachycardias can be difficult and controversial which is especially true for the focal origin. A focal mechanism is usually suggested by the centrifugal activation pattern of the tachycardia on the electroanatomic maps. The mechanism most commonly is microreentry, non-reentrant types are usually caused by enhanced automaticity or triggered activity. The latter tachycardias are not so common; the prevalence probably does not exceed 10% of all ATs.

Following segmental pulmonary vein isolation and partially after wide area antral ablation with confirming electrical isolation these tachycardias are typically focal in nature and related to recovered PV conduction, [3, 17, 18]. In our series, it was 60 % of all ATs.

Centrifugal activation pattern does not exclude reentrant mechanism by itself. This pattern can also be obtained from the exit site of a slowly conducting isthmus of a reentrant circuit, especially if the resolution of mapping is not high enough. Gerstenfeld *et al.* performed a detailed pharmacologic and entrainment testing in a group of patients presenting focal ATs following PVI. These maneuvers demonstrated that most of these ATs were due to localized small reentry circuits anchored to the slow conduction areas caused by the previous ablation. Only one of six ATs showed typical focal characteristics suggesting non reentrant mechanism. [19]. Similarly, Deisenhofer reported a series of LA ATs, using PVI plus additional lines during the first procedure. More than one third of these tachycardias were due to small reentrant circuits related to reconnected PVs [6]. Shah *et al.* [20], demonstrated that 73% of ATs developing after AF ablation in their study were related to narrow, critical isthmuses at the vicinity of previously ablated PV ostial sites. Slow conduction in these areas was crucial for maintaining

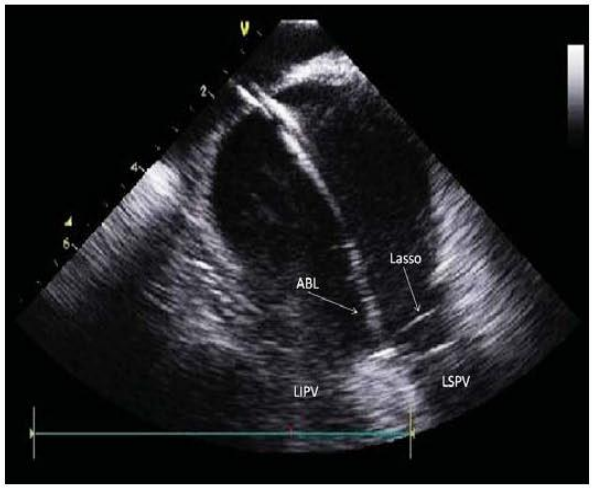

Fig. (1). Intracardiac echocardiography image of left atrium. Ablation catheter (ABL) is sitting on the carina between left superior (LSPV) and left inferior (LIPV) pulmonary veins. Lasso: circular catheter in LSPV.

such a small reentrant circuit. These were 10-18 mm in size and produced rapid centrifugal activation in the rest of the LA. Interestingly, these critical isthmuses characterized by low amplitude-long duration intracardiac electrograms occupied almost half of the tachycardia cycle length and coincided with the isoelectric intervals in all 12 ECG leads, between flutter waves. (Fig. **2**) These observations were highly consistent with the results of Yokokawa *et al*., [21] in terms of the observation that extremely slow conduction and adjacent anatomical barriers play a critical role in stabilizing these microreentrant circuits.

In the case of pulmonary vein tachycardia the pathologic impulse originates from the PV myocardial cells, and activates the LA through even a single recovered gap within the original lesion set. In the vast majority of cases, the rhythm within the PV is faster than in the LA, but sometimes 1:1 conduction can occur. After closing the gap(s) between LA and PV, the tachycardia should continue as a dissociated rhythm within the PV (Fig. **3**). The mechanism of these tachycardias is not clearly elucidated. Some data from the literature supported that the mechanism is non-reentrant due to enhanced automaticity and triggered

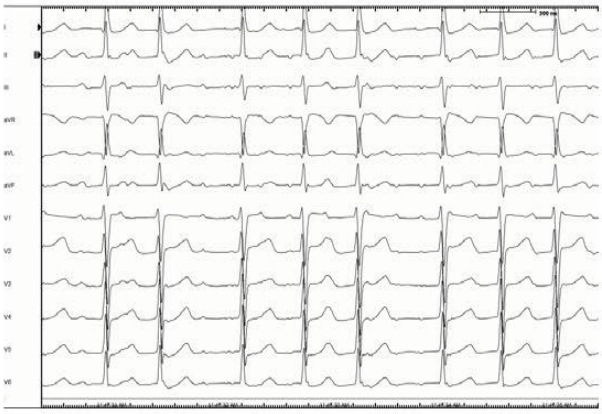

Fig. (2). Twelve lead surface ECG of a narrow isthmus reentry, originating from the vicinity of right inferior pulmonary vein. Note the long isoelectric interval between discrete flutter waves.

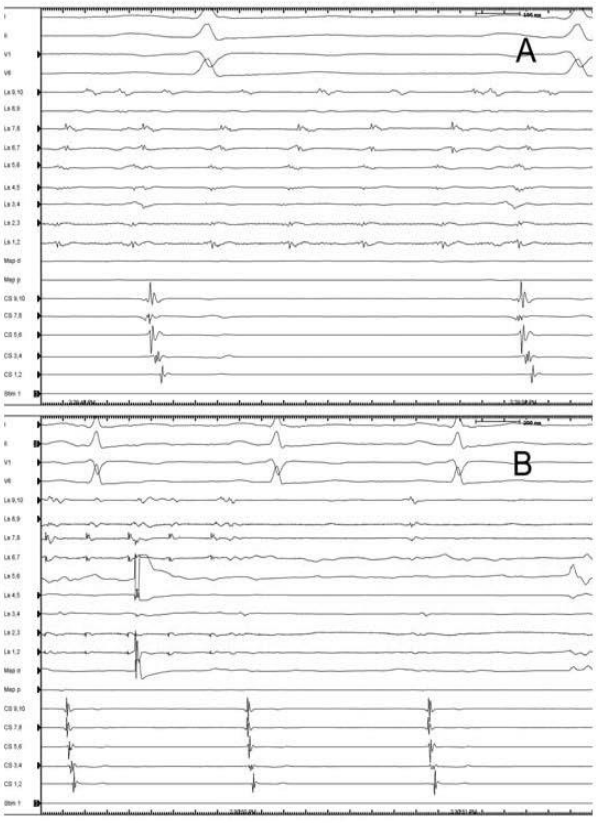

Fig. (3). Rapid, regular pulmonary vein tachycardia persists within an isolated right superior pulmonary vein. The atria, outside the isolated vein are in sinus rhythm. (A). Radiofrequency ablation at the earliest spot within the vein, indicated by the ablation artifact on the 4-5 bipoles of Lasso catheter results in the termination of tachycardia. (B) Ls: lasso catheter, CS: coronary sinus catheter, Map d: mapping catheter.

activity but others demonstrated evidences suggestive of reentry inside the pulmonary veins [17, 19].

Macroreentrant AT

Using anatomic ablation approaches with additional lines and/or CFAE ablation, the majority of ATs are macroreentrant, (73%-82%) which use regions of incomplete or recovered lesions and other anatomic obstacles. These tachycardias mostly revolve around the mitral valve (perimitral flutter, 28 % of cases in our experience) or less commonly around the isolated pulmonary venous ostia (roof dependent flutter, 12 % of cases), rarely around septal or posterior scars or LA appendage [18, 6]. The arrhythmia circuits of these ATs are usually independent from the PVs, but sometimes the myocardial sleeves within the veins can contribute to generating such a mechanism. Satomi *et al.* [22] as well as Robinson [23] presented clinical examples where the macroreentry circuits included the LA and PV myocardium as well, propagated via two conduction gaps located in the previous circular lesions which were relatively widely separated from each other (Fig. **4**). It should be noted that most of these tachycardias presented with focal pattern on three dimensional electroanatomic maps (3D EAM), and could have been misdiagnosed as classical focal AT without detailed entrainment mapping guided by multipolar catheter within the PVs.

Patients may also experience typical, cavo-tricuspid isthmus dependent right atrial flutter after AF ablation, which is not unusual in this population. The published prevalence of typical flutter is between 15%-30% [24, 25].

CLINICAL MANAGEMENT

The time interval between the index procedure and the emergence of organized ATs differs in published series [3, 6, 7, 17] but most commonly occurs relatively early, several weeks to months after the AF ablation procedure, not rarely during the "blanking period". Consequently, the initial treatment has to be conservative, considering that one third of ATs may resolve in time [7]. The mechanism of spontaneous restoration is not clearly elucidated, but probably related to healing and changing substrate following the ablation. The first task is to achieve an appropriate ventricular rate control, using beta blockers, digoxin or calcium channel blockers, but according to our observation, this strategy often fails. Electrical cardioversion can be more practical approach from the beginning, facilitated by using Class I or Class III antiarrhythmic agents, but-in agreement with Gerstenfeld *et al.*-if the tachycardia recurs beyond 2-3 months after first ablation, a repeated procedure is recommended [3].

Understanding the mechanism (see earlier) of the AT before the redo ablation procedure could facilitate the mapping and ablation strategy of the tachyarrhythmia. Twelve

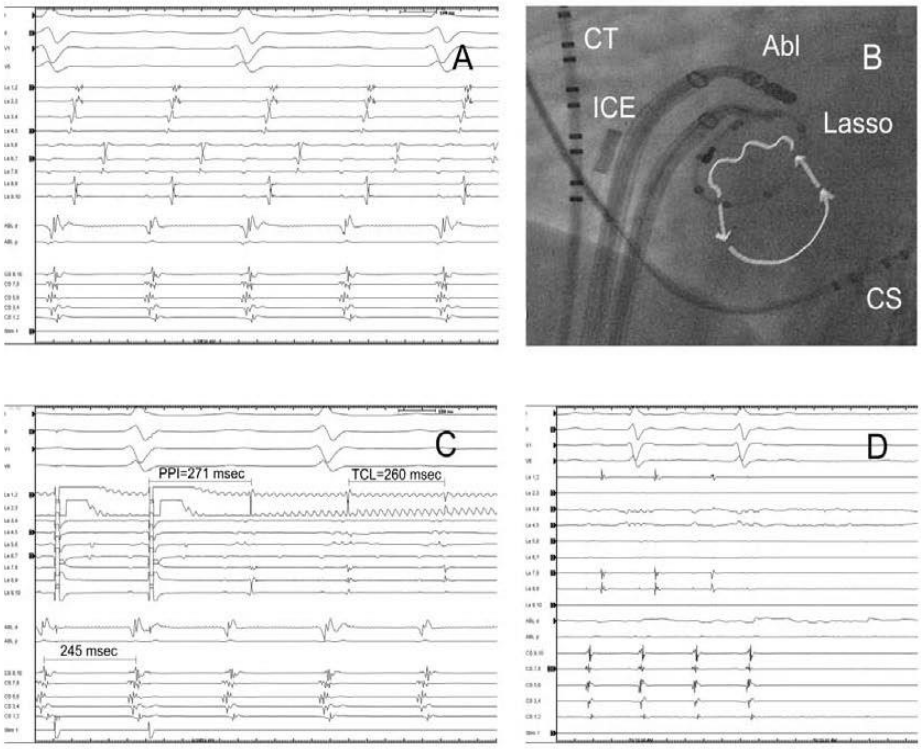

Fig. (4). Gap related tachycardia originating from the circular lesion around the right inferior pulmonary vein. (A, 200mm/sec), and the corresponding catheter positions, arrows point out the direction of activation through two gaps (at lasso pole number 4-5 and 7-8) in the ablation line (B). Entrainment pacing with 245 msec from the earliest lasso bipole (4-5) showed concealed fusion and PPI-TCL was 11 msec. (C). Termination of tachycardia during ablation at the entrance (pole 4-5) (D,100 mm/sec). The vein was isolated with the second ablation at the pole 7-8 (not shown). RIPV: right inferior pulmonary vein, CT: crista terminalis catheter, ICE: intracardiac echocardiography probe, Abl: ablation catheter, Lasso: lasso catheter, CS: coronary sinus catheter, PPI: post pacing interval, TCL: tachycardia cycle length.

lead surface ECGs can be helpful to distinguish between macroreentrant and focal arrhythmias: continuous activation is typical for macroreentrant mechanism, whilst isoelectric baseline between P waves suggests focal arrhythmias [20]. As we already pointed out, in case of separated P waves with long isoelectric intervals in all 12 leads one can anticipate a narrow isthmus reentry, caused by little electrical activity of slowly conducting isthmuses, coinciding with isoelectric lines. Some authors demonstrated that focal AT tends to be faster, than macroreentrant tachycardias [26], but others reported the opposite [24] or found no difference between them [13]. P wave morphology can be useful to localize the source of the arrhythmia but this is very much dependent on preexisting scarring and the extent of previous ablation. This is why it might be more useful after AF ablation restricted to PVI, without substrate modification. Focal ATs originating from the proximity of PVs or inside the veins are typically positive in V1, and across the precordium. ATs from left PVs usually generate P waves that are flat in lead I, lead II<III, negative in aVL and showing M shape in V1 comparing to right venous origin which are mostly positive in lead I, lead II>III, and biphasic in aVL, with late positive peak in V1.

In the electrophysiology laboratory, during an ongoing AT, our approach is to use multipolar catheters in the right atrium and coronary sinus (CS) and try to entrain the tachycardia first from the cavo-tricuspid isthmus (CTI) to exclude the possibility of typical right atrial flutter. After LA ablation of AF, sometimes typical atrial flutter shows atypical ECG findings [27] as for instance upright flutter waves in the inferior leads, which incorrectly suggests left atrial origin. However, this pacing maneuver may prevent unnecessary instrumentation of left atrium.

After exclusion of CTI dependent flutter or other right atrial sources, entrainment pacing is suggested from the distal and proximal electrodes of coronary sinus catheter. If the post-pacing interval (PPI) minus tachycardia cycle length (TCL) is shorter than 30 msec. from those poles following termination of pacing which has resulted in atrial capture, the presence of perimitral flutter is very likely.

Pascale *et al.* [28] reported that the patterns and timing of CS activation provide a rapid stratification of most likely macroreentrant ATs. In patients with proximal to distal CS activation, the whole spectrum of possible AT mechanisms was observed and in distal to proximal CS activation the majority (61%) were clockwise peri-mitral AT. They described also other two CS activation patterns defined as "chevron" or "reverse chevron" when the activations recorded on both the proximal and distal CS dipoles were latest or earliest, respectively, and those patterns were associated mostly with roof-dependent macroreentry.

Once a left atrial access is obtained, atrial tachycardias can be mapped by endocardial activation mapping and/or entrainment mapping. To exclude focal tachycardias related to PV reconnection, mapping of the four pulmonary vein ostia using circular catheter is recommended. If the mechanism is small or narrow isthmus reentry - which confines usually to typical reconnection sites of PVs, (septal aspect of right, and anterior sites of left PVs) [29] - entrainment pacing will show intracardiac evidence of concealed fusion and PPI≈TCL from a limited area, demonstrating mid-diastolic or long fractionated electrograms. Using 3D EAM, small reentry is considered when the majority of the cycle length can be accounted for during mapping and the diameter of the circuit is <3 cm. Re-isolation of PV(s) usually leads to termination of tachycardias.

Focal non-reentrant atrial tachycardia shows radial spread of activation from a point source and the activation mapping fails to account for the majority of tachycardia cycle length [18]. Endocardial activation at the source is presystolic, generally limited to the second half of diastole. Clinically more often paroxysmal than persistent as opposed to reentrant rhythms typically show 20-40-msec variability in cycle length. If the PV origin can be excluded, activation mapping has to be extended to typical sites of focal AT in LA, like posterior wall, LA appendage, and mitral annulus.

The macroreentry is considered when the tachycardia is entrained with "in circuit" response from remote sites of LA, electrograms span all or most of the diastole, activation mapping accounts for at least 85% of the tachycardia cycle length, as well as the diameter of the reentry circuit is >3 cm, and continuous propagation sequence with earliest and latest activation adjacent to each other on the EAM [24, 30].

The most common form is the peri-mitral flutter traversing the mitral isthmus.

In case of single loop peri-mitral circuit, there are several options to produce linear ablation lesions to terminate the tachycardia. The most common choice is the classical mitral isthmus line between the left inferior PV and the posterior mitral annulus (MA). Usually, it is a fairly long and concave isthmus, where one can have difficulties getting good contact without using intracardiac echocardiography. Histological data confirmed that coronary sinus muscle sleeves in this location are present in up to 75% of patients, and extend onto LA isthmus musculature. Not surprisingly, coronary sinus ablation is required in at least 70% of patients but bidirectional block cannot always be achieved [31]. Another possibility is to create linear lesion from the right inferior PV to posterior MA, which is one the most difficult isthmuses because of the proximity of three different anatomical structures (right and left atrium and coronary sinus) and the slow pathway region. Next option is drawing lines from the right superior PV to anterior MA. This isthmus is usually longer than the posterior mitral isthmus, and this line passes the insertion of Bachmann bundle, which is relatively thick and may prevent the creation of a transmural lesion (Fig. **5**). If we have multiloop circuits around the MA and right PVs, usually separate ablation lines are required to interrupt separate circuits, because of the aforementioned complexity of right posterior isthmus. In contrast, circuits around the MA and left PVs are much easier to ablate targeting the single left sided isthmus.

Completeness of mitral isthmus line is probably not always required for treating the tachycardia, but necessary to prevent them. Several studies pointed out that failure to achieve bidirectional mitral isthmus block increased the risk of developing left atrial flutter. Anouseh *et al.* demonstrated [32] that in patients in whom mitral isthmus block was not achieved, there was a fourfold risk of occurrence of subse-

quent ATs. Another question is whether these tachycardias are due to originally incomplete lines only or recovery of conduction. Sawney and co-authors [33] found that recovery of mitral isthmus conduction after initial achievement of block is common, 73 % and is associated with the emergence of peri-mitral flutter in 32%. They concluded that using electrophysiological endpoints alone might not be enough for maintaining long term results and at least in some patients it would be best to avoid mitral isthmus ablation if possible.

Macroreentry tachycardias around the isolated right of left side veins are less common, and in most patients completion of LA roof line leads to termination of tachycardias (Fig. **6**).

Regarding the practical aspects of ablation process, either during the mapping or pacing, the tachycardia can be terminated or transformed to another tachycardia(s), which complicates the procedure significantly. If such changes are pre-

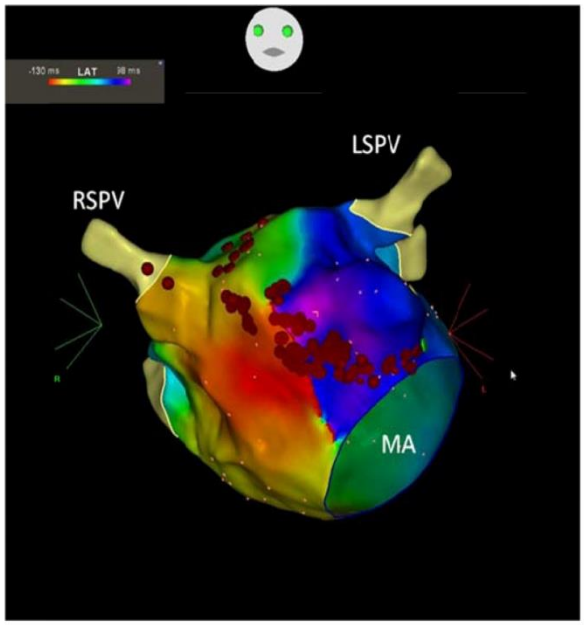

Fig. (5). Perimitral reentry propagating around the mitral valve in counterclokwise direction on three dimensional CARTO activation map. Red dots represent the ablation line which was created between the anterior mitral annulus and the right superior pulmonary vein. MA: mitral annulus, RSPV: right superior pulmonary vein, LSPV: left superior pulmonary vein.

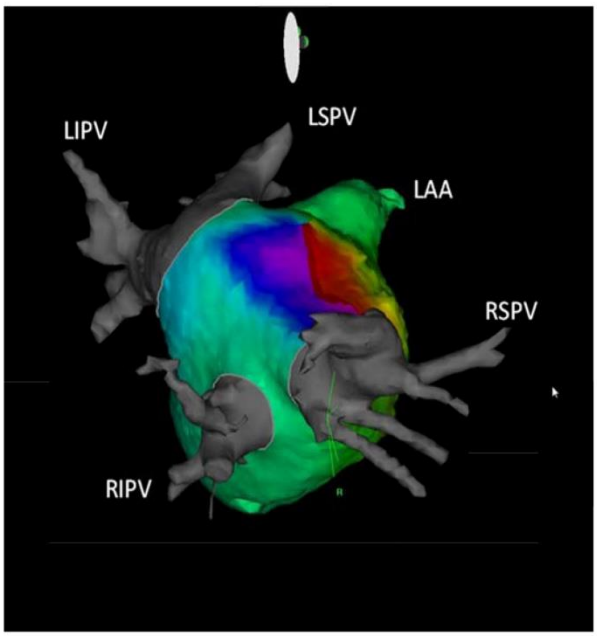

Fig. (6). Roof dependent flutter propagating around the right sided pulmonary veins on three dimensional CARTO activation map with CT integration in right lateral view. RSPV: right superior pulmonary vein, RIPV: right inferior pulmonary vein, LSPV: left superior pulmonary vein, LIPV: left inferior pulmonary vein, LAA: left atrial appendage.

dictable, isolation of reconnected PVs first is acceptable, since this is one of the major aims of procedure to prevent AF recurrence. Also, organized ATs related to gaps around PVs will be eliminated by this approach. Following the isolation of PVs if the tachycardia still persists or is inducible, entrainment and electroanatomic mapping can be carried out again, or otherwise empiric lesions can be applied.

SUMMARY

ATs occur relatively frequently after AF ablation procedures. The incidence of these tachycardias varies in the context of previous lesion set and probably of the extent of abnormal atrial electrophysiologic substrate. The mechanism in vast majority of cases is reentry related to gaps in prior ablation lines. Conservative therapy is usually not effective; radiofrequency ablation procedure is mostly successful but can be challenging and requires a complex approach.

CONFLICT OF INTEREST

The authors confirm that this article content has no conflicts of interest.

ACKNOWLEDGEMENTS

Declared none.

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Received: September 25, 2013 Revised: September 25, 2013 Accepted: April 05, 2014

III

J Interv Card Electrophysiol (2015) 44:113–118
DOI 10.1007/s10840-015-0032-2

Impaired adaptation to left atrial pressure increase in patients with atrial fibrillation

Gergely Ágoston[1] · Judit Szilágyi[1] · Gábor Bencsik[1] · Cristina Tutuianu[1] · Gergely Klausz[1] · László Sághy[1] · Albert Varga[1] · Tamás Forster[1] · Róbert Pap[1]

Received: 11 April 2015 / Accepted: 15 June 2015 / Published online: 30 June 2015

Abstract
Background or purpose Episodes of left atrial (LA) pressure increase predispose to atrial fibrillation (AF). The adaptation of LA mechanical function and electrophysiology to pressure elevation in healthy adults, and in patients with AF, is largely unknown.
Methods Eleven patients with left-sided accessory pathway (controls) and 16 patients with paroxysmal AF undergoing catheter ablation were studied. LA pressure (LAP) was recorded through transseptal catheterization, while speckle tracking-derived peak LA longitudinal strain (PALS) was measured using transthoracic echocardiography. Stiffness index (SI) was calculated as mean LAP/PALS. Effective refractory period (ERP) of the LA was determined during simultaneous atrioventricular (AV) pacing and during atrial pacing.
Results At baseline, AF patients had higher LA pressure (mean LAP 8.3±4.7 vs. 5.1±3.1 mmHg, p=0.048), reduced LA mechanical function (PALS 15.1±5.1 vs. 21.6±6.2 %, p=0.006, SI 0.69±0.75 vs. 0.28±0.22, p=0.015), and longer LA ERP (242.3±33.4 vs. 211.7±15.6 ms, p=0.017). Mean LAP was increased to the same extent by AV pacing in controls and AF patients (mean change 12.6±7.4 vs. 12.6±7.5 mmHg, p=0.980). At the same time PALS decreased (from 15.1±5.1 to 11.6±3.3 %, p=0.008), SI increased (from 0.69±0.75 to 1.29±1.17, p<0.001) and ERP shortened (from 242.3±33.4 to 215.9±26.3 ms, p=0.003) in AF patients, while they remained unchanged in controls.
Conclusions The stiffened LA in patients with AF responds to acute pressure elevation with an exaggerated increase in wall tension and decrease in ERP, which is not seen in the normal LA. This may underlie the propensity for AF during episodes of atrial stretch in these patients.

Keywords Atrial fibrillation · Left atrial pressure · Mechanoelectric feedback · Left atrial strain

✉ Róbert Pap
pap.paprobert@gmail.com

[1] 2nd Department of Medicine and Cardiology Centre, University of Szeged, Semmelweis str. 6., 6725 Szeged, Hungary

1 Introduction

Atrial pressure elevation predisposes to atrial fibrillation (AF) by several mechanisms. Acute atrial pressure increase leads to electrophysiologic changes, while chronic atrial stretch also induces structural remodeling.

In animal models, acute atrial dilatation has been shown to decrease atrial effective refractory period (ERP), result in slowing and block of impulse conduction and increased AF vulnerability [1–3]. This response has been termed atrial mechanoelectric feedback [4]. Similar changes have been described during acute pressure elevation by some [5–7] but not by others [8–10] in the human right atrium. However, the relation between atrial pressure and ERP has not been studied in the human left atrium (LA), the major source of AF.

Structural changes occur in the atria of patients with septal defect, mitral valve disease, hypertension, and heart failure even before the first detected episode of AF [11–14]. These changes are mediated by increased hemodynamic load on the atria. Chronic atrial stretch-induced remodeling includes atrial dilatation, fibrosis, loss of contractile elements, and a propensity for AF [15]. Structural remodeling results in a decline of the reservoir function of the LA, which can be estimated by the echocardiographic measurement of peak atrial longitudinal strain (PALS) during ventricular systole. In patients with

AF, PALS has been shown to correlate with the degree of LA fibrosis [16], thromboembolic risk [17], and the likelihood of sinus rhythm maintenance both after cardioversion [18] and catheter ablation [19]. However, the effect of LA pressure on PALS has not been determined.

Our aim was to study the responses in electrical (mechanoelectric feedback) and reservoir function to acute pressure elevation in the normal human LA and in the LA of patients with AF.

2 Methods

2.1 Study group

Consecutive patients with manifest or concealed left-sided accessory pathway, without a history of AF (controls) and patients with paroxysmal AF scheduled for pulmonary vein isolation, who had no symptomatic and/or documented AF episodes in the week prior to the procedure, were included. Exclusion criteria were persistent AF, $CHADS_2$ (Congestive Heart Failure, Hypertension, Age, Diabetes, Stroke [Doubled]) score >2, previous LA ablation or open heart surgery, heart failure, reduced left ventricular function, and moderate to severe mitral regurgitation.

2.2 Electrophysiologic procedures

Informed consent was obtained and antiarrhythmic drugs have been discontinued for at least five half-lives at the time of the procedure. Using right ± left femoral vein access single (control patients) or double (AF patients) transseptal puncture was performed using 8.0 or 8.5 French transseptal sheaths (Fast-Cath, St. Jude Medical, St. Paul, MN, USA), under intracardiac echocardiographic guidance. The side arm of the transseptal sheath was connected to a disposable pressure transducer (Combitrans, B. Braun, Melsungen, Germany), which was positioned and zeroed at a reference level 5 cm below the left sternal border, at the fourth intercostal space [20]. Pressure was recorded at a sampling rate of 977/s by the CardioLab EP Recording System (GE Healthcare, Chalfont St Giles, UK).

2.3 Pacing protocol

The protocol was performed after the completion of the catheter ablation procedure, during the waiting period. At each site, pacing was performed with 2-ms stimulus duration, at twice diastolic threshold. Simultaneous atrioventricular (AV) pacing was carried out to produce an acute increase in LA pressure. LA ERP was determined both during simultaneous AV pacing and during atrial pacing at the same cycle length to control for the effect of the preceding cycle length on atrial ERP (Fig. 1). In AF patients, the atrial pacing catheter was positioned in the LA appendage; while in control patients, LA ERP was determined by pacing from the distal bipole of the coronary sinus (CS) catheter to avoid the need for a second transseptal puncture. This has been previously shown to reflect LA ERP well [21, 22]. Simultaneous AV pacing at a cycle length of 500 ms was carried out for at least 3 min to allow stabilization of pressure. Then, after every 30th drive stimulus progressively more premature (5-ms steps) atrial stimuli were introduced, without a pause in the drive train. LA ERP was defined as the longest coupling interval of the extrastimulus that failed to capture the atrium twice in succession.

2.4 Echocardiographic measurements

All patients underwent comprehensive two-dimensional transthoracic echocardiography examination using a commercially available ultrasound machine (Vivid I, GE Medical Systems, Horten, Norway) equipped with a 2.5–3.5-MHz phased array transducer and software application for two-dimensional speckle tracking-based strain imaging.

LA volumes were calculated using the biplane method of disks (modified Simpson's rule), in the apical 4- and 2-chamber view at end-systole (maximum LA size), and a mean value of volume was obtained [23]. LA volumes were indexed (LAVI) to body surface area (BSA). Mitral annular velocity was evaluated by tissue Doppler in the pulsed-wave mode [24].

2.5 Assessment of left atrial reservoir function

Particular attention was paid to obtain an adequate two-dimensional-grayscale image, allowing obvious delineation of LA wall and extracardiac structures. The frame rate was set between 60 and 80 frames per second. Three consecutive heart cycles were recorded at baseline and immediately after simultaneous AV pacing (Fig. 2). Recordings were processed using acoustic-tracking software (EchoPac PC version 110.1.8, GE Healthcare, Horten, Norway), allowing off-line semiautomated analysis of speckle tracking-based strain [25]. In the end-diastolic/systolic frame, the atrial endocardial border was marked by a point-and-click method. After automatic creation of a region of interest, the LA wall was divided into six regions, and segmental tracking quality was analyzed (Fig. 2). The reference point was set at the onset of the QRS, and the average positive peak atrial longitudinal strain (PALS), which corresponds to LA reservoir function, was measured (Fig. 2). Values from the three consecutive cycles

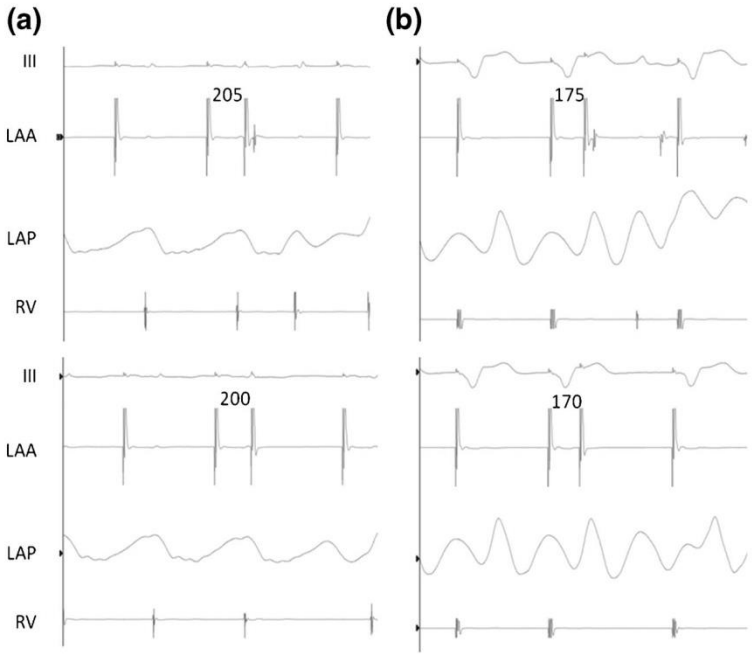

Fig. 1 Determination of LA effective refractory period (ERP) during atrial pacing (**a**) and during simultaneous AV pacing (**b**). *LAA* LA appendage, *LAP* left atrial pressure, *RV* right ventricle. Coupling intervals (CI) of extrastimuli are shown in milliseconds. ERP is defined as the longest CI without atrial capture

were averaged [26]. The LA stiffness index (SI) was calculated as mean LA pressure (LAP)/PALS [27].

2.6 Statistical analysis

Continuous variables are presented as mean±standard deviation and were tested for normality using the Kolmogorov-Smirnov test and compared by the Student's *t* test or Mann-Whitney test as appropriate. Categorical variables are expressed as percentage and compared using the chi-square test. All statistical analyses were performed using SPSS software (SPSS Inc., Chicago, IL, USA). A p value <0.05 was considered statistically significant.

3 Results

3.1 Clinical characteristics and baseline values of the two groups

Eleven patients undergoing left-sided accessory pathway ablation (controls) and 16 patients with paroxysmal AF were included. Controls were younger and had smaller LA volume index (LAVI), without further differences in clinical characteristics (Table 1).

Patients with AF had higher mean (mLAP) and peak (pLAP) invasive LA pressures at baseline (8.3±4.7 vs. 5.1±3.1 mmHg, p=0.048 and 20.8±8.8 vs. 14.6±5.7 mmHg, p=0.015, respectively), compared to controls. Baseline LA PALS was significantly lower (15.1±5.1 vs. 21.6±6.2 %, p=0.006),

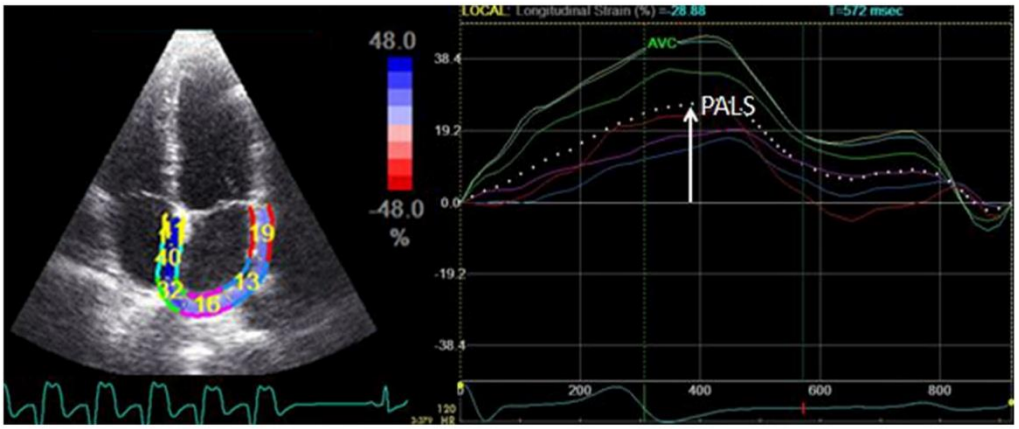

Fig. 2 Measurement of peak atrial longitudinal strain (*PALS*) immediately after simultaneous AV pacing. The *dashed curve* represents the average PALS

Table 1 Baseline clinical and echocardiographic parameters

	Controls	AF patients	*p* value
Age (year)	42.2±21.1	60.3±8.8	0.019
Female (%)	22	31	0.629
BSA (m^2)	1.91±0.22	1.98±0.22	0.381
Hypertension (%)	27	56	0.137
Diabetes (%)	0	0	
$CHADS_2$ score	0.22±0.44	0.75±0.68	0.084
LVEF (%)	64.7±6.8	59.8±3.7	0.189
E_a (cm/s)	12.0±2.6	10.4±3.3	0.331
LAVI (ml/m^2)	32.4±11.4	59.4±12.1	<0.001

BSA body surface area, *LVEF* left ventricular ejection fraction, E_a mitral annulus early diastolic velocity, *LAVI* LA volume indexed to BSA

while baseline SI was higher (0.69±0.75 vs. 0.28±0.22, p=0.015), pointing to diminished LA reservoir function in patients with AF. At the same time, LA ERP was longer at baseline in AF patients, compared to controls (242.3±33.4 vs. 211.7±15.6 ms, p=0.017).

3.2 Left atrial pressure elevation

During simultaneous AV pacing, mLAP rose by the same extent in controls and AF patients (mean change 12.6±7.4 vs. 12.6±7.5 mmHg, p=0.980). At the same time, LA PALS decreased (from 15.1±5.1 to 11.6±3.3 %, p=0.008) and SI increased (from 0.69±0.75 to 1.29±1.17, p<0.001) in patients with AF, while they remained unchanged in controls (from 21.6±6.2 to 22.9±7.1 %, p=0.405 and from 0.28±0.22 to 0.45±0.43, p=0.10, respectively). With pressure elevation, LA ERP decreased in AF patients (from 242.3±33.4 to 215.9 ±26.3 ms, p=0.003) but was not changed significantly in controls (from 211.9±16.7 to 206.3±19.6 ms, p=0.276) (Fig. 3).

3.3 Follow-up

Four of 16 AF patients (25 %) experienced arrhythmia recurrence after pulmonary vein isolation, during 16±7 months of follow-up. Patients with recurrence had lower baseline LA reservoir function (PALS = 10.7±3.2 vs. 16.7±4.0 %, p=0.036), compared to those without.

4 Discussion

4.1 Main findings

We could not show the operation of mechanoelectric feedback or a change in the reservoir function of the normal LA during acute pressure elevation. We have seen, on the other hand, a dramatic fall in ERP and reservoir function in response to

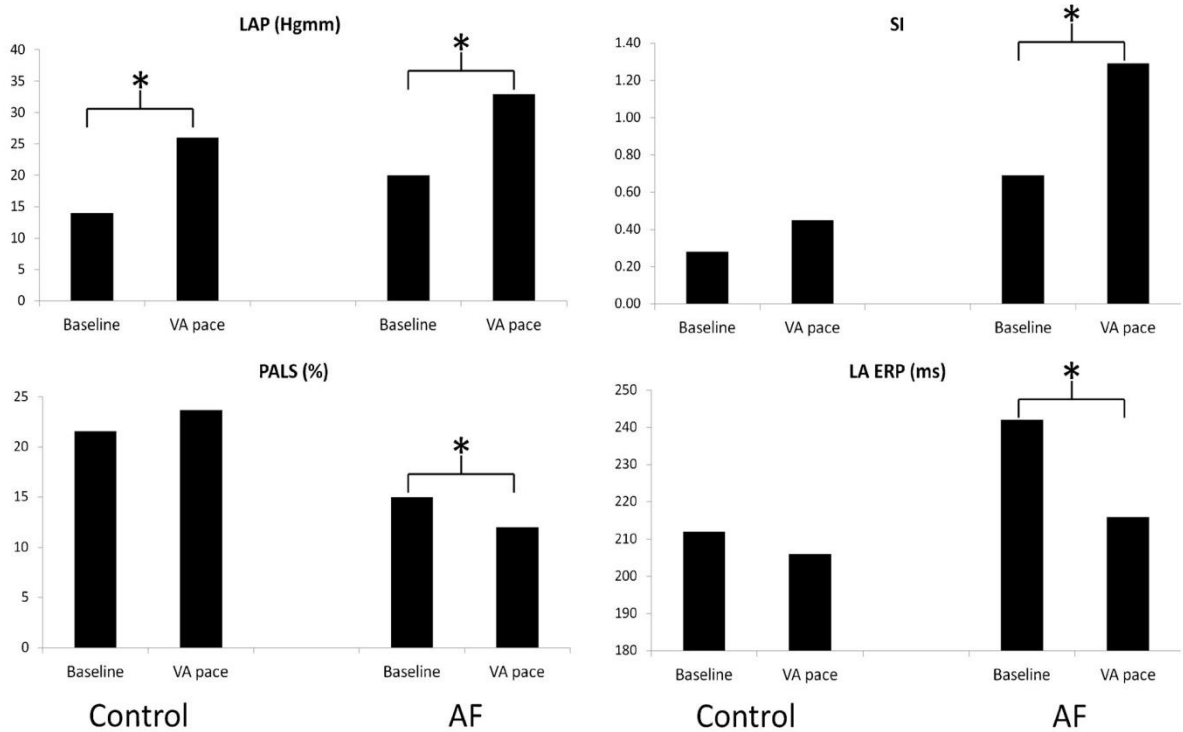

Fig. 3 Changes in mean LA pressure (*LAP*), LA strain (*PALS*), stiffness index (*SI*), and refractory period (*ERP*) in response to simultaneous AV pacing in controls and AF patients. *Stars* mark significant (p<0.05) changes

pressure rise in patients with AF. We conclude that the normal adaptation to acute elevations in LA pressure is lost in patients with AF, even during sustained sinus rhythm.

Even when in sinus rhythm, patients with paroxysmal AF show diminished LA reservoir function estimated by LA strain [28, 29]. We have shown in this study that LA strain is also dependent on LA pressure in patients with AF, and an acute rise in pressure leads to a decline in LA reservoir function and increased stiffness, a response not observed in the normal LA.

In patients with paroxysmal AF, but without a recent episode, LA ERP measured at the LA appendage has been shown by some [30, 31], but not by other reports [32] to be longer than in controls, while it was consistently shorter in patients with persistent AF. The reason for this inconsistency might be the dependence of atrial refractoriness on pressure, a phenomenon known as mechanoelectric feedback [4].

Mechanoelectric feedback is well described in the ventricles, has been shown at the atrial level and in the human right atrium, but has not been studied in the human LA, the major source of AF [5–8, 33]. Acute atrial stretch increases vulnerability to AF in both animal models and humans [1, 34]; the mechanism most commonly considered behind this is a shortening of refractoriness and slowing of impulse conduction [2, 4, 6, 35], both promoting the development of reentry. We have shown in this study that pressure-related shortening of refractoriness—mechanoelectric feedback—is magnified in the LA of patients with AF, which likely facilitates the persistence of the arrhythmia.

Paroxysmal AF itself leads to atrial pressure elevation [36]. According to our study, increased atrial pressure can result in increased stiffness and wall tension with shortened atrial refractoriness favoring AF maintenance. This way, a vicious circle is established, which may culminate in persistent AF.

4.2 Limitations

Due to inherent differences between the patient populations and procedures, the control and AF groups could not be well matched in all baseline characteristics. Therefore, the main outcome of this study was not the absolute value of electrical and mechanical parameters but rather the difference in the magnitude of pressure-related change between the two groups. Subjects in the control group were slightly younger, related to differences in the typical age of presentation of the two arrhythmias. Therefore, it cannot be excluded that some of the baseline differences between groups are also age-related. However, our paroxysmal AF population was otherwise relatively healthy and comparable in other clinical parameters to the control group, except for AF-related LA remodeling. The pacing protocol was carried out after ablation, during the waiting period for ethical reasons, to avoid prolonging left atrial access. It cannot be excluded that more extensive ablation in the AF group influenced the results. However, ablation in these patients was limited to the posterior LA, around the pulmonary veins (PVs), which is a region that is relatively immobile due to tethering by PVs, and this part of the LA is not included in echocardiographic strain analysis.

5 Conclusions

The normal LA can adapt to episodes of acute pressure elevation without a substantial change in reservoir function and ERP. On the other hand, patients with AF show an exaggerated fall in their already diminished LA reservoir function in response to pressure rise, with an out of proportion increase in wall tension leading to a decline in LA ERP, which likely further promotes the development of AF.

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IV

J Interv Card Electrophysiol (2016) 45:29–35
DOI 10.1007/s10840-015-0070-9

Association between dissociated firing in isolated pulmonary veins and the initiation and maintenance of atrial fibrillation

Cristina Tutuianu[1] · Vassil Traykov[2] · Gábor Bencsik[1] · Gergely Klausz[1] · László Sághy[1] · Robert Pap[1]

Received: 29 June 2015 / Accepted: 14 October 2015 / Published online: 21 October 2015

Abstract
Background Whether dissociated firing (DiFi) in isolated pulmonary veins (PVs) implies arrhythmogenicity of the particular PV and, therefore, a better outcome of PV isolation (PVI) for paroxysmal atrial fibrillation (PAF) is debated.
Methods Thirty-one patients undergoing their first PVI for PAF were studied. Isoproterenol was infused for induction, and the triggering PV was identified. During sustained PAF, sequential recordings were made with a decapolar circular mapping catheter from each PV. The dominant frequency (DF) was determined using fast Fourier transformation. Spontaneous DiFi was monitored for 30 min after PVI.
Results PAF was triggered by the PVs in all patients. Fourteen (45 %) patients had DiFi after PVI in at least one PV. It was recorded most commonly from the left upper (84 %) and lower (67 %), less commonly from the right upper (31 %) PV. Out of the 23 PVs with DiFi, 13 (57 %) showed sporadic ectopic beats while 10 (44 %) had sustained ectopic rhythm or isolated tachycardia. There was no difference in size between PVs with or without DiFi (5.9±1.2 vs. 5.6±1.0 cm ostial perimeter, p=0.40). Triggering PVs more commonly showed any DiFi, compared to nontriggering PVs (68 vs. 27 %, p=0.003) and more commonly had sustained DiFi (53 vs. 0 %, p<0.001). During PAF PVs with any DiFi showed faster maximal DF compared to PVs without DiFi (7.1±1.3 vs. 5.9±1.1 Hz, p=0.001). Higher maximal DF was recorded in PVs with sustained versus sporadic DiFi versus PVs without DiFi (7.5 ±0.9 vs. 6.8±1.6 vs. 5.9±1.1 Hz, respectively, p=0.002). Patients with DiFi after PVI had a longer mean time to recurrent PAF compared to those without DiFi (52 vs. 32 months, p=0.048).
Conclusions Dissociated firing in isolated PVs is associated with their role in the initiation and maintenance of PAF.

Keywords Atrial fibrillation · Dissociated firing · Triggering pulmonary vein

1 Introduction

Pulmonary vein (PV) ectopy is recognized as a common trigger for the initiation of paroxysmal atrial fibrillation (PAF) [1]. Furthermore, a role for PVs in the maintenance of PAF has been suggested by frequency mapping [2]. Thereby, durable PV isolation (PVI) is a highly effective therapy when PV arrhythmogenicity is responsible for PAF. However, when other mechanisms are involved, the effectiveness of PVI may be limited [3].

After achieving PVI, dissociated firing (DiFi) from PVs is frequently observed [4]. The capability of PVs to generate an isolated ectopic rhythm may signify their arrhythmic potential and therefore predict a higher success [5]. On the other hand, the presence of DiFi may be related to better quality of PVI, farther away from PV ostia, also suggesting improved outcome [6]. Whether spontaneous electrical activity of isolated PVs is related to their arrhythmogenicity or only an epiphenomenon and whether observing DiFi after PVI has prognostic significance remain unclear. The purpose of this study was to investigate the association between DiFi and PV arrhythmogenicity by frequency mapping during PAF.

✉ Cristina Tutuianu
tutucris2008@yahoo.com

[1] 2nd Department of Medicine and Cardiology Center, University of Szeged, Semmelweis str. 6, 6725 Szeged, Hungary

[2] Tokuda Hospital, Sofia, Bulgaria

2 Methods

2.1 Patient characteristics

Thirty-one consecutive patients undergoing their first PVI for drug-refractory, symptomatic PAF (53±9 years old, 17 men) were prospectively studied. All patients gave their written informed consent to participate in the study. Exclusion criteria were previous left atrial (LA) catheter ablation or open-heart surgery, persistent AF, severe valvular heart disease, or LA thrombus. Patients without inducible sustained PAF during the study (two patients) and those with PAF triggers originating from extra-PV sites (two patients) were also excluded.

2.2 Electrophysiologic procedure

Patients were on oral anticoagulation for at least 3 weeks before the ablation, and transesophageal echocardiography was performed to exclude any atrial thrombi before the procedure. All antiarrhythmic drugs were discontinued for at least five half-lives except amiodarone which was discontinued 1 month prior to the procedure. The study was performed as described previously [2]. Briefly, under conscious sedation (midazolam ±fentanyl), following femoral venous access, two decapolar steerable catheters (interelectrode spacing 2–5–2 mm, Dynamic Deca; Bard Electrophysiology, Lowell, MA, USA) were positioned in the coronary sinus and the posterolateral right atrium. The left atrium (LA) and the PVs were mapped through double transseptal puncture. Intracardiac echocardiography (ICE) (AcuNav; Acuson Corp., Mountain View, CA, USA) was used for performing the transseptal puncture and to guide catheter positioning. A decapolar circular mapping catheter (CMC) (Inquiry Optima; St. Jude Medical, Irvine, CA, USA) and a 3.5-mm irrigated-tip mapping catheter (Navistar Thermocool; Biosense Webster, Diamond Bar, LA, USA) were advanced into the LA.

2.3 Assessment of the triggering PVs and signal analysis

The CMC was positioned at the left PV antrum overlying both left PVs, and the mapping catheter was positioned on the right PV carina. If the patient presented in sinus rhythm, PAF was induced by isoproterenol infusion, starting at 3 μg/min with incremental doses of 5 μg/min until PAF was induced, the maximum dose of 20 μg/min was reached, or the patient developed side effects. If the patient was in AF, first, we performed transthoracic electrical cardioversion before PAF induction. Ectopic activity triggering a PAF episode was identified, and the origin was determined based on the endocardial activation sequence and by comparison to paced activation sequences from PVs as well as observing LA-PV electrogram reversal as previously described [2]. Triggering activity was considered to originate from the right PVs when earliest activation and LA-PV electrogram reversal were recorded using the mapping catheter at the right PV carina. When earliest activation was recorded using the CMC, left upper or lower PV origin was determined based on the radiographic position of poles recording the earliest activity. After induction, isoproterenol administration was stopped and further recordings were made after a 5-min washout period. During sustained PAF, the CMC was used to record sequentially from each PV ostium. Signals were recorded for at least 30 s at a sampling rate of 997 Hz using a digital EP recording system (GE CardioLab; General Electric, Milwaukee, WI, USA) and were stored for offline analysis. Intracardiac recordings were analyzed, utilizing a custom-designed computer application prepared with the LabView software package (National Instruments, Austin, TX, USA). Signals were filtered between 30 and 500 Hz, rectified, and low-pass filtered at 20 Hz. A fast Fourier transformation (FFT) was performed on two consecutive 5-s episodes from each bipole of the CMC. The frequency spectrum in the 3–15 Hz range was obtained, and the peak with the highest power was determined as the dominant frequency (DF). Noisy and highly disorganized signals (organization index<0.25) were excluded from the analysis [2]. The DFs of consecutive 5-s episodes were averaged, and the maximum DF value of all bipoles was taken as the DF of that PV and used for analysis (Fig. 1).

2.4 Pulmonary vein isolation

Contiguous ablation lesions were delivered using the irrigated catheter (with a power setting of 25–35 W and 15 ml/min irrigation) to encircle ipsilateral PVs in pairs, with the end point of elimination or dissociation of PV potentials. Additional ablation inside the encircling lesion was delivered when needed to achieve this end point.

2.5 Assessment of DiFi

After electrical disconnection of all PVs, each PV was assessed periodically during a 30-min waiting period for the presence of DiFi. The CMC was positioned in one PV for 30 s and then moved to the next, repeating periodically during the waiting period. Rhythm in the PV was classified as follows: 1=absent (if there was no electrical activity at all), 2=sporadic DiFi (scarce and fortuitous occurrence of dissociated potentials without a regular rhythm), and 3=sustained DiFi (regular ectopic rhythm or isolated PV tachycardia) (Fig. 1b, c).

2.6 Measurement of the PV ostial area

The LA and PVs were segmented from high-resolution computed tomography (CT) volumes using the CARTO system (Biosense Webster, Baldwin Park, CA, USA), and cut planes were positioned to separate the PVs from the body of the LA.

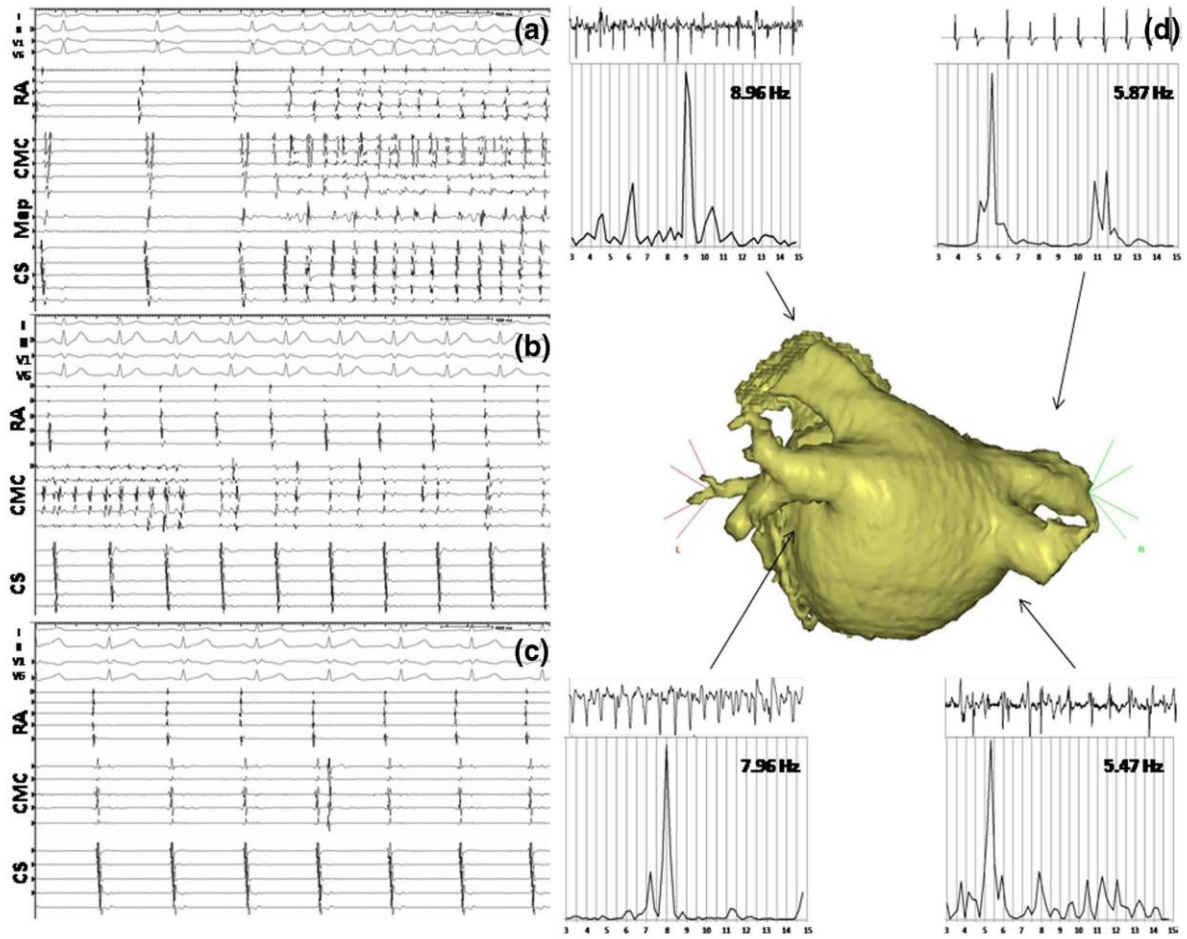

Fig. 1 Surface ECG leads I, II, V_1, and V_6, together with intracardiac recordings from the right atrium (*RA*) and circular mapping catheter (*CMC*) placed in the left pulmonary vein antrum (**a**), left superior pulmonary vein (LSPV, **b**), and left inferior pulmonary vein (LIPV, **c**) and from the proximal to distal coronary sinus (*CS*). Atrial fibrillation is initiated by rapid discharge from the LSPV (**a**). Following isolation of the vein, sustained dissociated rhythm with intermittent burst activity was recorded (**b**). Sporadic dissociated activity was recorded in the LIPV after isolation (**c**). In the right pulmonary veins, there was no dissociated activity after isolation. Dominant frequency (DF) distribution during sustained atrial fibrillation in the same patient (**d**)

Using area measurement tools of the CARTO system, we measured the cross-sectional area and the perimeter of the ostium of the PVs. We chose to determine the area of the ostium of PVs because it can be measured with greater precision than the mean diameter [7].

2.7 Follow-up and redo procedures

All patients had a follow-up visit at 3, 6, and 12 months. Seven-day Holter monitoring was performed when a patient had no symptoms at least 6 months after ablation to reveal asymptomatic recurrence or when patients reported symptoms suggestive of recurrence without documented arrhythmia. In case of recurrence, patients were offered a second procedure, during which reisolation of reconnected PVs was performed. No additional ablation of non-PV triggers or substrate outside the PV antra was undertaken. Since permanent isolation of PVs often requires a second attempt, we evaluated the success of PVI after the last procedure and defined it as freedom from any sustained (>30 s) atrial arrhythmia (symptomatic or asymptomatic), off antiarrhythmic drugs.

2.8 Statistical analysis

Continuous variables are reported as mean±SD and compared using one-way analysis of variance (ANOVA) and Student's *t* test. Categorical variables are presented as percentage and compared using the chi-square test. Kaplan-Meier survival analysis was used to estimate the mean time to recurrent AF after the procedure. Survival curves were compared using the log-rank test. All statistical analyses were performed using the SPSS software version 16 (IBM Inc., NY, USA). A p value <0.05 was considered statistically significant.

3 Results

3.1 Patient characteristics and incidence of DiFi after PVI

Baseline characteristics of the patients from the study group are presented in Table 1. PAF triggers were found to originate from the left superior PV (LSVP) in 20 (65 %) patients, from the left inferior PV (LIPV) in 5 (16 %) patients, and from the right PVs in 6 (19 %) patients. Electrical isolation of PVs by circumferential ablation was achieved in all patients. Fourteen (45 %) patients had DiFi after PVI in at least one and 7 of them in more than one PV. It was recorded most commonly from the left upper (84 %) and lower (67 %) and less commonly from the right upper (31 %) PVs. Out of the 23 PVs with DiFi, 13 (57 %) showed sporadic ectopic beats while 10 (44 %) had sustained ectopic rhythm or isolated tachycardia. No further ablation was performed to abolish this dissociated rhythm. There was no difference in size between PVs with or without DiFi (5.9±1.2 vs. 5.6±1.0 cm ostial perimeter, p=0.40, and 2.7±1.1 vs. 2.4±0.9 cm^2 ostial area, p=0.55).

3.2 Association between PV triggers and DiFi

Triggering PVs more commonly showed any DiFi, compared to nontriggering PVs (68 vs. 27 %, p=0.003) and more commonly had sustained DiFi (53 vs. 0 %, p<0.001) (Fig. 2). Thus, the triggering vein was more likely to have dissociated ectopy after isolation.

3.3 Association between DF and DiFi

During sustained PAF, PVs with any DiFi showed faster maximal DF compared to PVs without DiFi (7.1±1.3 vs. 5.9±1.1 Hz, p=0.001). Higher maximal DF was recorded in PVs with sustained versus sporadic DiFi versus PVs without DiFi (7.5±0.9 vs. 6.8±1.6 vs. 5.9±1.1 Hz, respectively, p=0.002) (Fig. 3). The maximal DF was higher in triggering PVs, compared to nontriggering ones (8.02±1.64 vs. 6.53±1.36, p<0.001).

Table 1 Clinical characteristics of patients with and without dissociated firing (DiFi) after pulmonary vein isolation for paroxysmal atrial fibrillation (PAF)

Variable	No DiFi	DiFi	p value
Age (years)	54±9.6	52±8.5	0.27
Men (%)	41	71	0.19
PAF duration (months)	63.5±53.3	58.9±67.4	0.42
Hypertension (%)	65	69	0.79
Coronary disease (%)	6	8	0.84
Diabetes (%)	12	8	0.71
Left atrial diameter (mm)	45.08±3.4	45.45±6.9	0.43
LVEF (%)	61±6.28	64.81±6.54	0.08

LVEF left ventricular ejection fraction

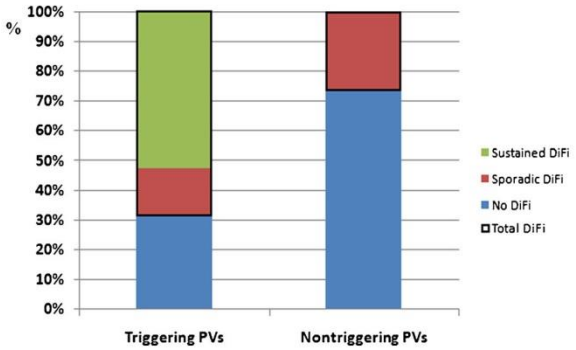

Fig. 2 Distribution of the different types of dissociated firing (*DiFi*) following isolation in pulmonary veins (*PVs*) with atrial fibrillation triggers versus nontriggering PVs

3.4 Clinical outcome

During the ablation procedure and a mean of 31±18 months of follow-up, no major complication occurred in any patient. Ten patients (32 %) underwent a redo PVI procedure, and all of them had reconnected PVs which were reisolated. There was no difference in the redo rate between groups (29 vs. 35 %, p=0.690, for patients with and without DiFi, respectively). Two patients (14 %) with DiFi and seven patients (41 %) without DiFi had a recurrence after the last procedure. One of the two patients with DiFi had asymptomatic recurrence and refused a second procedure. The difference in recurrence rate did not reach statistical significance (p=0.101). However, patients with DiFi after PVI had a longer mean time to recurrent PAF after the last procedure compared to those without DiFi at the index procedure (52 vs. 32 months, p=0.048) (Fig. 4).

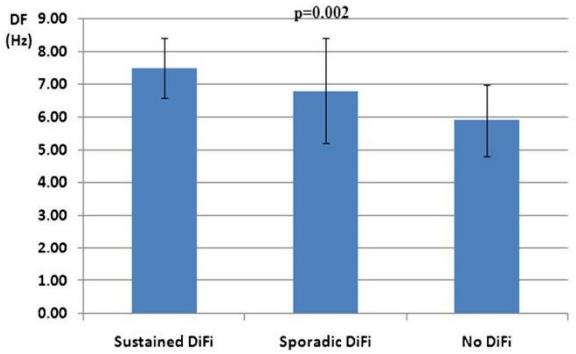

Fig. 3 Dominant frequency (DF) during atrial fibrillation in pulmonary veins showing different types of dissociated firing (*DiFi*) after isolation

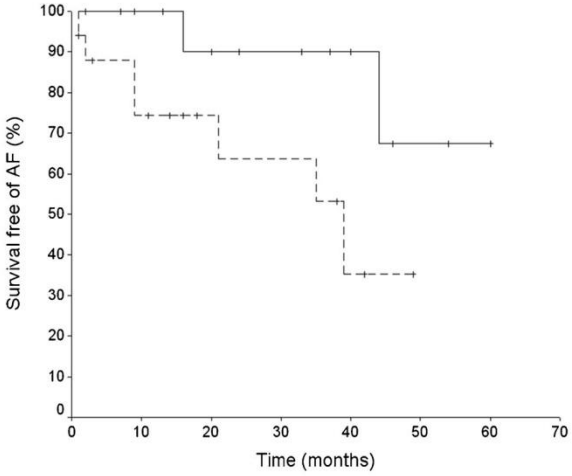

Fig. 4 Kaplan-Meier curve of the freedom from arrhythmia recurrence. Patients with dissociated firing (DiFi) after pulmonary vein isolation (*continuous line*) had a longer mean time to recurrence compared to those without DiFi (*broken line*)

4 Discussion

4.1 Major findings

The main finding of our study is that PVs with DiFi after isolation show higher activation rate during fibrillation and, therefore, are more likely to have a role in the perpetuation of atrial fibrillation as compared to PVs without DiFi. Furthermore, PVs showing DiFi more frequently initiate atrial fibrillation. Therefore, DiFi after PVI can be considered a hallmark of PV arrhythmogenicity pointing to the role of the particular PV both in the initiation and maintenance of PAF. When PAF is initiated and maintained by PV arrhythmogenicity rather than other mechanisms, PVI should have a better outcome.

4.2 Mechanism of DiFi

Spontaneous electrical activity of PVs after isolation presents as DiFi. It is either an escape rhythm overridden by the faster sinus node (SN) before isolation and unmasked by PVI or rapid ectopic triggering no longer capable of initiating PAF after isolation. Specialized cells resembling those of the SN have been described in the PVs and are thought to be responsible for spontaneous automaticity [8, 9] manifested as DiFi after PVI, which shows a pharmacological response similar to sinus rhythm [10]. However, PV electrical activity triggering PAF may have a mechanism that is different from the slow escape rhythm type of DiFi. Its mechanism is more compatible with triggered activity [11], being provoked by rapid pacing and the autonomic effects of adenosine [12], rather than being suppressed. This type of activity most commonly is eliminated by circumferential ablation around the PVs, possibly due to the effects of ablation on the autonomic nervous system [13]. Therefore, the association between DiFi and PV arrhythmogenicity deserves further investigation.

4.3 Incidence of DiFi after PVI

The incidence of DiFi after PVI shows a broad variation from 2.8 to 92 % [10, 14]. This variation may be explained by differences in the definition of dissociated activity, study population, or ablation approach. Kabra et al. [14] reported an incidence of 92 % of DiFi after PVI for PAF, and similar to our study, the DiFi was classified as isolated ectopic beats, ectopic regular rhythm, or PV fibrillation. In contrast, Buiatti et al. [15] in a recent study reported that 27 % of their patients had at least one vein (12 % of PVs) with DiFi, but the investigators took a unique approach to define the dissociated activity (slow intermittent potentials without a regular rhythm) and excluded most of what we have defined as DiFi. In our study, the incidence of DiFi was 45 % of PAF patients presenting for PVI. Consistent with a previous study [16], we observed a higher proportion of DiFi originating from superior PVs compared to inferior veins. Also, PAF was triggered most commonly from upper PVs, similar to previous reports [17]. This may be related to thicker muscle sleeves [18]. Guerra et al. [19] linked areas of PV wall thickening to high-frequency potentials and the origin of ectopic beats. We could not find any significant correlation between the size of PVs and the presence of dissociated activity after isolation.

The ablation technique also has an impact on the occurrence of DiFi after PVI. Segmental, ostial isolation resulted in a DiFi rate of 5–33 % [4, 20], while wide-area encircling ablation resulted in up to 85–92 % [14, 21, 22]. This suggests that ablation closer to or inside the PV ostium (e.g., at the carina) can destroy some of the foci responsible for DiFi.

4.4 Prognostic implications of DiFi

Similar to the above mentioned reports defining the incidence and characteristics of DiFi, studies on the impact of dissociated activity on the outcome of PVI are also conflicting. Some have shown improved outcome of PVI in patients with DiFi [5, 6] and better success rate when the foci of DiFi were ablated inside the PVI lesions, rather than left untouched [23]. However, others have reported either no difference [15, 16, 22] or even increased recurrence rate in the case of DiFi that is not ablated [23]. The explanation for an improved success rate in the aforementioned studies is either that DiFi is a marker of more proximal and better quality ablation lesions, providing evidence of exit block from the PVs [6] or that DiFi is a marker of PV arrhythmogenicity [5].

4.5 Relation between DiFi and PV arrhythmogenicity

Although, in two previous studies, the association between triggering PVs and DiFi was assessed [15, 22], a systematic approach to PAF induction was not employed and the proportion of patients with the triggering structure identified was low (10 and 44.5 %, respectively). Furthermore, the definition of triggering and DiFi was variable. One of these studies [15] suggested an association between PVs with PAF triggers and DiFi, while in the other, it was not significant [22]. We included only patients with the triggering PV identified (defined as the vein from which ectopic activity initiated PAF) and observed a significantly higher incidence of DiFi after isolation of a triggering PV, compared to nontriggering ones. This suggests that PVs with DiFi after PVI are more likely to have a role as initiators of PAF.

We previously described [2] that triggering PVs showed the fastest activity during sustained PAF, pointing to their role not only in the initiation but also in the perpetuation of the arrhythmia. In this study, we observed that PVs with DiFi showed faster maximal DF during PAF compared to PVs without DiFi, suggesting an association between DiFi and the maintenance of PAF. In addition, the correlation between DiFi and arrhythmogenicity of a PV both as initiator and perpetuator of PAF became more pronounced with more expressed (sustained vs. sporadic) DiFi. In line with the above and similar to studies showing DiFi to be a positive predictor of success [5, 6], we found that patients with DiFi after PVI had a longer mean time to recurrent PAF compared to those without DiFi.

These results confirm that observing DiFi from isolated PVs is related to the arrhythmogenicity of the PV. The presence of DiFi is associated with a better outcome of PVI not because the quality of PVI is higher but because it implies that PAF is more likely to have a PV-based mechanism for the particular patient. On the contrary, patients without DiFi after PVI are more likely to have non-PV mechanisms and more advanced atrial substrate involved in the arrhythmia. This is further supported by previous studies finding more structural heart disease [4, 24], hypertension [5], and non-paroxysmal atrial fibrillation [24] among cases without DiFi and a trend for a lower left ventricular ejection fraction in this study (Table 1).

4.6 Limitations

This study has several limitations. First, only patients in whom PAF could be induced and originated from the PVs were included; thereby, the real incidence of DiFi, including those without inducible PAF and non-PV triggers, may be different. Second, the localization of PV triggers was done with approximation, because of the limited number of catheters available in the left atrium, due to ethical considerations. However, in our previous study, this method showed accurate detection of arrhythmogenic PVs [2]. Third, some patients received ablation at the PV carina which could have destroyed some of the foci responsible for DiFi. Fourth, the PVs were sequentially and intermittently checked for DiFi during the 30-min waiting period. It is possible for sporadic DiFi to be missed during the repositioning of the CMC. Fifth, the effect of the CMC on some observed DiFi cannot be completely ruled out. Sixth, pharmacological challenge was not employed to induce DiFi in silent veins after PVI. Although adenosine can rarely induce ectopic beats in isolated PVs, it mostly has a suppressant effect on DiFi [10, 12]. Isoproterenol is known to decrease the cycle length of DiFi [10] but never has been shown to induce DiFi in silent PVs. Since cycle length was not part of the definition of DiFi, the lack of isoproterenol testing after PVI was not expected to influence our results. Furthermore, our aim was to clarify the implications of spontaneous DiFi, a common finding after empirical PVI. Finally, the sample size was limited and this may have accounted for the lack of a statistically significant difference in success rates.

4.7 Clinical implications

The present study demonstrates an association between PV arrhythmogenicity and DiFi. PVs with DiFi are more likely to have a role as initiators and perpetuators of PAF and therefore deserve meticulous care in isolation and PVI verification (e.g., pace-capture or adenosine testing of the ablation lesion) to improve the long-term outcome of the procedure. On the contrary, in patients without DiFi after PVI, a more thorough search for non-PV mechanisms of arrhythmogenesis might be justified.

Conflict of interest The authors declare that they have no competing interests.

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Received: 7 March 2018 | Revised: 7 October 2018 | Accepted: 23 October 2018

DOI: 10.1111/jce.13779

ORIGINAL ARTICLE

WILEY

Is adenosine useful for the identification of atrial fibrillation triggers?

Cristina Tutuianu MD | Robert Pap MD, PhD | Tamas Riesz MD | Gabor Bencsik MD, PhD | Attila Makai MD, PhD | Laszlo Saghy MD, PhD

2nd Department of Medicine and Cardiology Centre, University of Szeged, Szeged, Hungary

Correspondence
Cristina Tutuianu, MD, 2nd Department of Medicine, Cardiology Center, University of Szeged, Semmelweis Str. 6, Szeged 6725, Hungary.
Email: tutucris2008@gmail.com

Disclosures: None.

Abstract

Introduction: Both isoproterenol (Iso) and adenosine (Ado) are used to induce atrial fibrillation (AF) in the electrophysiology lab. However, the utility of Ado has not been systematically established.

Objective: The purpose of this study was to compare Ado to Iso for the induction of paroxysmal AF.

Methods: Forty patients (16 women; mean age, 60 ± 12 years) with paroxysmal AF, presenting for ablation were prospectively included of whom 36 (90%) received Ado (18-36 mg) and/or Iso (3-20 μg/min incremental dose) in a randomized order (26 [72%] received both drugs).

Results: AF was induced with Iso in 15 of 32 (47%) and with Ado in 12 of 30 (40%) patients ($P = 0.9$). Iso-triggered AF started from the left pulmonary veins (PVs) in 11 of 15 (73%), from the right PVs in 3 of 15 (20%), and from the coronary sinus (CS) in 1 of 15 (7%) cases. Ado-induced AF episodes originated from the left PVs in 6 of 12 (50%), from the right atrium (RA) in 4 of 12 (33%), and from the CS in 2 of 12 (17%) cases. Altogether, Iso-induced AF was more likely initiated from the PVs (93%) compared with Ado (50%) ($P = 0.02$). Ado-induced non-PV triggers were not predictive of arrhythmia recurrence after PV isolation.

Conclusion: Ado much more frequently induces non-PV triggers, especially from the RA. The clinical significance of these foci, however, is questionable.

KEYWORDS
adenosine, atrial fibrillation, isoproterenol, pulmonary vein, triggers

1 | INTRODUCTION

Elimination of initiating triggers has become the cornerstone of atrial fibrillation (AF) treatment. Most of these triggers reside in the pulmonary veins (PVs)[1]; however, non-PV triggers are an important source of recurrence after PV isolation (PVI). Triggers can be identified during the electrophysiology study if spontaneously occurring or can be induced by a drug challenge. Owing to the spurious nature of spontaneous triggers and the laboriousness of AF provocation, empirical isolation of all PVs has become the standard in AF ablation, despite the fact that selective isolation of only the triggering PV can achieve similar success in selected patients.[2] Even if total PV isolation is pursued as a first step, identification of non-PV triggers gains importance when AF occurs despite isolated PVs.[3,4] The role of high dose isoproterenol (Iso) infusion to elicit AF triggers is well established.[5,6] Besides Iso, adenosine (Ado) or adenosine triphosphate (ATP) is increasingly used for the induction of AF, despite the lack of systematic studies on the sensitivity and

Cristina Tutuianu and Robert Pap have contributed equally to the manuscript.

specificity of these drugs. We sought to determine the utility of Ado in identifying triggers of paroxysmal AF by comparing it to Iso in a prospective, randomized study.

2 | METHODS

2.1 | Study population

Sample size estimation was based on a previous pilot analysis of retrospective data.[7] In this, we found marked differences in the location of triggers disclosed by Iso and Ado: only PV triggers were induced with Iso, while non-PV triggers were seen in 88% of those receiving Ado also. Expecting less pronounced a difference: 20% vs 80% non-PV trigger rate with Iso vs Ado, respectively, and an 80% induction rate for both drugs, the sample size for an α value of 0.05 and a power of 0.8 would be 15 patients tested with each drug. Due to dropouts and a lower induction rate during the study, altogether 40 patients were enrolled, with the aim being to test at least 30 patients with each drug.

All 40 patients (16 women; mean age, 60 ± 12 years) had paroxysmal AF and were referred for catheter ablation. The study was approved by the institutional review board of the University of Szeged (no. 41-83). All patients gave their written informed consent to participate in the study. Exclusion criteria were previous left atrial (LA) catheter ablation or open heart surgery, persistent AF, severe valvular heart disease, or LA thrombus.

Patients were prospectively included and received Ado and Iso for induction in a randomized order.

2.2 | Electrophysiologic procedure

Patients were on oral anticoagulation for at least 3 weeks before the ablation and all antiarrhythmic drugs were discontinued for at least five half-lives except amiodarone, which was discontinued 1 month before the procedure. Patients presented in the lab in sinus rhythm or in AF for ablation. In the case of AF before the induction protocol, direct current cardioversion (DCCV) was performed. The study was performed under light conscious sedation with midazolam ± fentanyl, as described previously.[8,9] In brief, after femoral venous access two decapolar steerable catheters (interelectrode spacing 2-5-2 mm; Dynamic Deca; Bard Electrophysiology, Lowell, MA) were positioned in the coronary sinus (CS) and the posterolateral right atrium (RA) with the distal pole in the superior vena cava. Double transseptal punctures were performed to access the left atrium (LA). Intracardiac echocardiography (AcuNav; Acuson Corp., Mountain View, CA) was used to guide the transseptal puncture and catheter positioning. A decapolar circular mapping catheter (CMC) (Inquiry Optima; St Jude Medical, Irvine, CA) was positioned at the left PV antrum overlying both left PVs, and a 3.5-mm irrigated-tip mapping catheter (Navistar Thermocool; Biosense Webster, Diamond Bar, CA) was positioned on the right PV carina (Figure 1).

2.3 | Drug challenge

If the patient presented in AF, DCCV was performed to restore sinus rhythm and evaluate for spontaneous reinitiation and identifying postcardioversion AF triggers. If the presenting rhythm was sinus or AF was not spontaneously reinitiated after the cardioversion, we proceeded with the drug challenge.

Iso was infused via a short femoral venous sheath in incremental doses starting at 3 μg/min and increasing after 3 to 5 minutes to 5, 10, 15 μg/min, and a maximum dose of 20 μg/min, until induction of AF or intolerable side effects occurred.

Ado was administered into the RA via one long transseptal sheath that was pulled back in the RA. A quick bolus of 18 mg was given flushed with 5 to 10 mL of saline. A second dose of 36 mg was administered if AF was not induced after the first dose. Ectopic activity triggering an AF episode was identified and the origin determined based on the endocardial activation sequence, as previously described.[8,9] Triggers of AF were considered to arise from the left PVs if the earliest activation and LA-PV electrogram reversal were recorded on the CMC and from the right PVs if the earliest atrial activation was recorded on the mapping catheter positioned at the right PV carina. If earliest atrial activation during bursts of ectopic activity initiating AF was recorded at any of the CS or RA bipoles, then these structures were identified as the origin of triggers (Figure 2).

The order in which the two drugs were administered (Iso first or Ado first) was randomized in a 1:1 fashion. When sustained AF was induced and did not terminate after a few minutes, DCCV was performed and the second drug was administered after a 5-minute waiting period. In cases when immediate recurrence of AF (IRAF) occurred after DCCV, drug challenge was terminated and we proceeded with ablation. We determined the effectiveness of the two drugs in inducing AF and compared them with each other and spontaneous AF episodes in terms of the location of AF triggers.

2.4 | Catheter ablation

After creation of a three-dimensional electroanatomic shell of the LA, circumferential, irrigated radiofrequency ablation lesions were created around ipsilateral PVs using the mapping catheter, with the endpoint of electrical isolation manifested in exit and entrance block between LA and PVs. The decision to selectively isolate only the left or right PVs, whichever were shown to be arrhythmogenic during drug challenge, or empirically isolate all four PVs was at the discretion of the operator. However, in case of a redo procedure, all four PVs were isolated, irrespective of the initial approach.

2.5 | Statistical analysis

Continuous variables are expressed as mean ± SD and compared using Student t test. The categorical variables are reported as a percentage and compared using χ^2 analysis. All statistical analyses

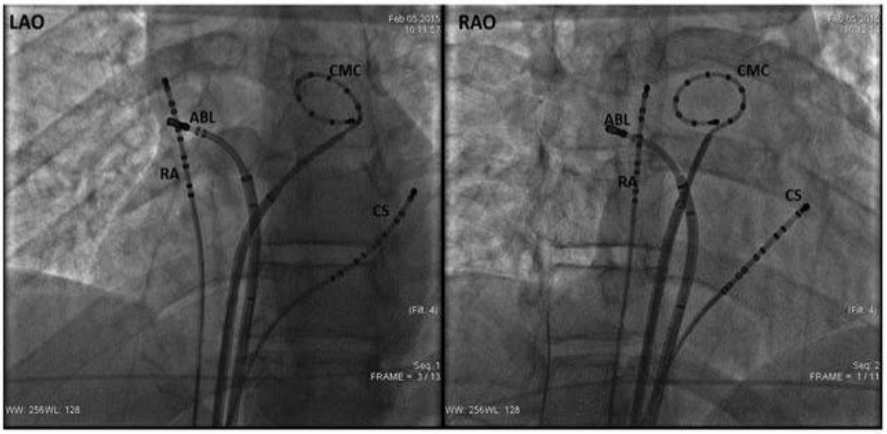

FIGURE 1 Left anterior oblique (LAO) and right anterior oblique (RAO) view showing the two decapolar catheters placed in the coronary sinus (CS) and right atrium (RA), circular mapping catheter (CMC) in the left pulmonary veins (PVs), and mapping catheter (ABL) in right PVs

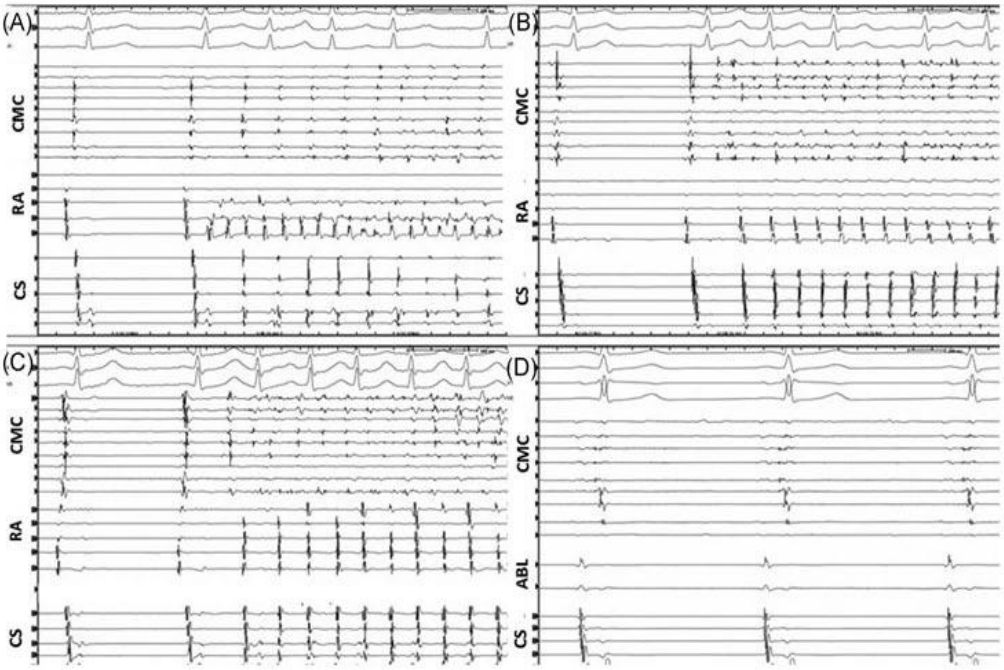

FIGURE 2 Surface electrocardiogram leads I, II, V6 along with intracardiac recordings from the right atrium (RA), coronary sinus (CS), and circular mapping catheter (CMC) placed in the pulmonary vein (PV) antrum, during initiation of atrial fibrillation. (A) During adenosine infusion AF was induced from RA. Spontaneously (B) and during isoproterenol infusion (C) AF was induced from the PVs. Paper speed = 75 mm/s. During redo procedure, only the previous triggering pulmonary vein was reconnected (D). Paper speed = 100 mm/s

were performed using the SPSS software version 16 (IBM Inc., Armonk, NY). $P < 0.05$ was considered statistically significant.

3 | RESULTS

Four (10%) patients could not receive any drug challenge because their spontaneous AF ongoing at the commencement of the procedure restarted immediately after DCCV. Eighteen of the remaining 36 patients were randomized to receive Iso first and 18 Ado first. In 10 (28%) patients, the second drug was not given, because the AF induced by the first drug spontaneously restarted after DCCV. Therefore, 36 (90%) patients received their first and 26 of 36 (72%) patients the second drug. Altogether, 32 patients received Iso and 30 patients Ado (30 received 18 mg; 21 received 18 and 36 mg, respectively). AF was induced with Iso in 15 of 32 (47%) and with Ado in 12 of 30 (40%) patients ($P = 0.9$). Iso triggered AF started from the left PVs in 11 (73%), from the right PVs in three

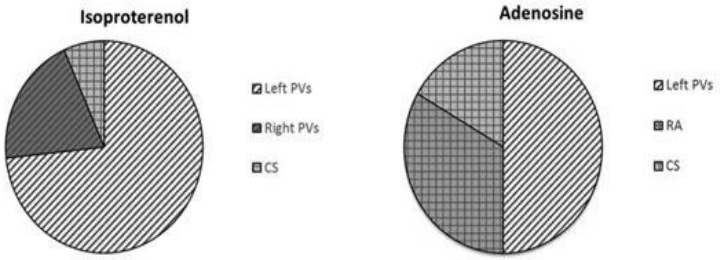

FIGURE 3 Trigger sites of isoproterenol induced AF (A) and adenosine induced AF (B)

(20%), and from the CS in one (7%) cases (Figure 3A). Ado induced AF episodes originated from the left PVs in six (50%), from the RA in four (33%), and from the CS in two (17%) cases (Figure 3B). Altogether, Iso induced AF was more likely initiated from the PVs (93%), compared with Ado (50%) ($P = 0.02$).

Of the 26 (72%) patients (Figure 4; Table 1) who received both drugs, AF could not be induced by drug challenge in 13 (50%). Iso triggered AF in 9 of 26 (35%) patients; all triggers were localized to the PVs (seven left and two right PVs). Ado was effective at inducing AF in 8 of 26 (31%), two from left PVs, and six from non PV sites (four RA, two CS; $P < 0.01$ vs Iso). Both drugs induced AF in 4 of 26 (15%) cases. In two of those four patients, triggers originated from the left PVs with both Iso and Ado, while in the remaining two cases there was discordance between the two drugs, Ado manifesting non PV triggers.

Fourteen (35%) patients had spontaneous AF during the procedure, 13 (93%) originated from the PVs (nine left, four right PVs), and only one from the CS. Ten of these cases received one or both drugs. Iso reproduced left or right PV triggers in 6 of 7 cases and was ineffective in one. Ado reproduced left PV triggers in four of seven cases but was ineffective in three. This results in a sensitivity to reproduce spontaneous triggers of 86% for Iso and 57% for Ado.

After drug testing, 38 of 40 (95%) patients underwent PVI. Two patients, for whom initially a selective PVI was planned, did not have an ablation (one was noninducible and one had RA trigger on Ado). Thirty of the remaining 38 (79%) received empirical isolation of all four PVs, while eight (21%) patients a selective PVI of arrhythmogenic PVs. Ten of 38 (26%) underwent a second PVI procedure with the aim of four PV isolation, because of recurrence of AF. After the last procedure, 32 of 38 (84%) ablated patients were free of recurrence during 16 + 9 months of follow up.

Of the 14 patients who had PV triggers disclosed by Iso infusion, one was lost to follow up, and the rest had no AF recurrence after the last PVI. In case of the only patient with a non PV trigger on Iso PVI was ineffective, even after a redo procedure. Among the six patients with PV triggers on Ado, PVI, and redo PVI failed in one. Of the six patients with non PV triggers on Ado, one was not ablated and one failed PVI and a redo. The remaining four are without recurrence after the last procedure. Therefore, while Iso was 100% accurate in predicting a favorable response to PVI, the accuracy of Ado challenge was only 55%.

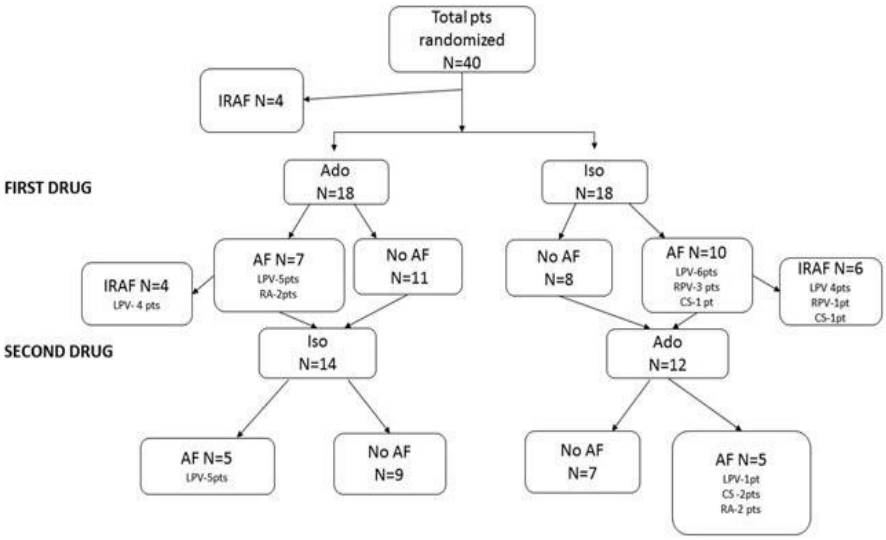

FIGURE 4 Study flowchart. Ado, adenosine; CS, coronary sinus; IRAF, immediate recurrence of atrial fibrillation; Iso, isoproterenol, LPV, left pulmonary veins, RA, right atrium; RPV, right pulmonary veins

TABLE 1 Characteristics of patients who received both drugs. Abbreviations are as on Figure 4

		Isoproterenol		Adenosine		
Patient #	First drug	Maximum dose, μg/min	Induced triggers	Maximum dose, mg	Induced triggers	Spontaneous triggers
1	Ado	10	LPV	18	RA	...
2	Ado	20	LPV	18	LPV	LPV
3	Iso	20	LPV	18	LPV	-
4	Iso	20	...	18	RA	...
5	Ado	20	...	18	RA	...
6	Ado	20	LPV	36	...	...
7	Ado	20	LPV	36	...	...
8	Iso	5	LPV	36	CS	...
9	Ado	20	LPV	36	...	...
10	Iso	15	RPV	36	...	RPV
11	Iso	3	LPV	36	...	LPV
12	Iso	20	...	36	...	...
13	Ado	20	...	36	...	...
14	Iso	20	...	36	...	...
15	Ado	20	...	36	...	LPV
16	Ado	20	...	36	...	...
17	Ado	20	...	36	...	...
18	Ado	20	...	36	...	...
19	Iso	20	...	36	...	...
20	Iso	20	...	36	...	...
21	Iso	20	...	36	...	...
22	Ado	20	...	36	...	...
23	Iso	20	...	36	CS	...
24	Ado	20	...	36	...	...
25	Iso	20	...	36	RA	...
26	Ado	20	...	36	...	...

Abbreviations: Ado, adenosine; CS, coronary sinus; Iso, isoproterenol; LPV, left pulmonary veins; RPV, right pulmonary veins.

There was no correlation between non-PV triggers induced by Ado and arrhythmia recurrence after the last procedure ($P = 0.90$).

4 | DISCUSSION

The main finding of this study is that, while Iso mostly induces PV triggers, Ado is more likely to induce non-PV triggers of AF, dominantly from the RA. Half of the Ado-inducible patients had AF from non-PV sites, compared with only 7% with Iso. Moreover, in two cases the two drugs showed divergent effects in the same patient: Ado inducing non-PV while Iso PV triggers.

While trigger sites disclosed by Iso challenge showed excellent correlation with the long-term response to PVI (no recurrence in case of PV triggers and recurrence in the single case of non-PV trigger), there was no such correlation seen with Ado, PVI being equally effective in those with PV or non-PV triggers induced by this drug.

4.1 | Comparison with previous studies

The use of Iso in the electrophysiology lab to study triggers of AF is well established.[5,6,9] It has been shown to effectively identify arrhythmogenic PVs that can selectively be ablated, achieving similar success to empirical four-PV isolation.[10] In contrast, Ado has mostly been used anecdotally for AF induction. A number of case reports have been published of triggers identified with Ado or ATP, most of which originated outside the PVs.[11–16] More investigators have used ATP to test for non-PV triggers after PVI.[17–19] Strikingly most of these studies originate from Asia, use ATP, and report a high rate of non-PV triggers.[20]

Tao et al[21] used ATP 20 mg for induction in patients with paroxysmal or persistent AF. They found that ATP induced AF in 30% of the cases and trigger sites were from the PVs in more than 80% of these. The higher rate of PV-triggering with ATP compared with our results with Ado may be explained by differences in the mode of action and relative doses of the two drugs. The molecular weight of

ATP is approximately three times that of Ado; therefore, the number of adenosine molecules in 20-mg ATP is much less than in 18 mg of Ado, the lower dose in our study. In contrast, ATP exerts a much more pronounced negative chrono- and dromotropic response due to its action on P2 receptors located in the left ventricle inducing a cardiocardiac vagal reflex.[22] The higher relative dose and exclusive action on adenosine (P1) receptors may explain the higher rate of RA triggers we saw with Ado.

Nevertheless, another report from Japan using ATP showed a higher rate of RA triggers. Hasebe et al[23] also used 20 mg of ATP after other methods of AF induction, including Iso, failed. More patients had RA triggers than PV triggers with ATP injection (six vs four) and frequency analysis suggested the driver reside in the RA during AF in those with RA triggers. These patients were younger and also more often had a family history of AF. The authors suggested they may have a distinct form of the arrhythmia, which they named RA fibrillation. However, it is possible that in Hasebe's study,[23] younger patients were more difficult to induce with other methods (including Iso) and, therefore, more likely to receive ATP. The higher rate of RA fibrillation in their case might be merely a manifestation of the preferential effect of ATP/Ado on the RA.[23]

The high percentage of RA triggers seen with Ado/ATP may be related to the drug's route of administration, short half-life, and mode of action. Ado/ATP is administered into a central vein or directly the RA, and therefore the concentration of the drug is higher in the RA than the LA, after having traveled through the lungs, where, due to its very short half-life, a great fraction may be eliminated. Moreover, the sensitivity of the RA to Ado is known to be higher than the LA,[24,25] explained by at least two-fold higher expression of the Ado receptor in the RA.[26] Receptor density in the RA has also been correlated to Ado-induced AF in humans.[26] Although direct injection of adenosine into the LA had been proposed, this was not done in this study, due to concerns of air embolism.[27]

4.2 | The relation between induced and spontaneous triggers

Few studies have compared induced and spontaneous AF. Lazar et al[28] analyzed atrial activation frequency distribution and found no difference between patients with spontaneous AF (three patients) and Iso-induced AF (13 patients), while Calvo et al[29] showed the same for pacing-induced AF. In the abovementioned study, Tao et al[21] found that the spontaneous AF initiation site was in the PVs in 96% of cases, while after ATP injection in 85%. Only in one of the four patients with a non-PV trigger manifested by ATP was there a correlation with the spontaneous site. In other words, they show, similar to our results, more non-PV triggers with ATP, compared with spontaneous AF, but the majority of those ATP-induced non-PV triggers were not clinical. We have seen four patients in whom Ado reproduced spontaneous AF, but none originated outside the PVs. Therefore, it seems that Ado/ATP may reproduce PV-triggers; however, the frequent non-PV triggers seen with these drugs cannot be correlated with spontaneous AF.

The question arises whether non-PV triggers induced by Ado are clinically relevant as initiators of spontaneous AF. Triggers of spontaneous AF in our and the above-mentioned reports[4,5,30] have been located to the PVs in more than 90% of the cases. The high percentage of non-PV AF-initiating sites seen with Ado is in sharp contrast with this observation.

5 | LIMITATIONS

The study has several limitations. First, the localization of PV triggers was done with approximation because of the limited number of catheters in the LA and RA. However, differentiating LA from RA and PV from non-PV triggers is straightforward with this catheter setup. After the first drug induced AF, we frequently (33% after Iso and 22% after Ado) encountered IRAF after cardioversion preventing us to administer the second drug. Therefore, the number of patients who received both Iso and Ado is relatively low.

6 | CLINICAL IMPLICATIONS

The literature on non-PV triggers of AF relies heavily on the use of Ado/ATP for induction, although the correlation with spontaneous AF has never been established. We show in a comparison with Iso before PVI that Ado much more frequently induces non-PV triggers, especially from the RA. The clinical significance of these foci, however, remains questionable as Ado induced non-PV triggers in some patients who had PV-triggers with Iso, and the concordance of non-PV triggers with spontaneous AF could not be documented. Moreover, the induction of non-PV triggers by Ado before PVI did not influence the success of the procedure. On the basis of the above, Ado cannot be recommended for the identification of trigger sites to guide catheter ablation of paroxysmal AF.

ORCID

Cristina Tutuianu http://orcid.org/0000-0003-0754-9584

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How to cite this article: Tutuianu C, Pap R, Riesz T, Bencsik G, Makai A, Saghy L. Is adenosine useful for the identification of atrial fibrillation triggers? *J Cardiovasc Electrophysiol*. 2019;30: 171–177. https://doi.org/10.1111/jce.13779